Docket No. 5/1275

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Gerald Juergen Roth et al.	Group Art Unit: 1624	
Serial No.:	09/678,682	Examiner: Hong Liu	
Filed:	Oct. 3, 2000	Confirmation No.: 6798	
Patent No.:	6,762,180		
For:	Substituted Indolines Which Inhibit Receptor Tyrosine Kinases		

PETITION UNDER 37 C.F.R. § 1.705(d) AND
REQUEST FOR RECONSIDERATION OF PATENT TERM ADJUSTMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Petitioners hereby request reconsideration of the final patent term adjustment ("PTA") for U.S. Patent No. 6,762,180 (the "'180 patent") (Exhibit 1 hereto) of 68 days. In place thereof, Petitioners request that the PTA be changed to 310 days.

Petitioners contend that the USPTO made three errors in determining the PTA published on the face of the '180 patent: (1) it improperly charged the Petitioners with responding to a Notice of Missing Parts 46 days beyond the 3-month date specified in 35 U.S.C. §154(b)(2)(C)(ii) when, in fact, the response was filed well before the 3-month date; (2) it failed to reduce the PTA by 86 days, the time by which Petitioners' December 8, 2003, response to the Office Action of June 13, 2003, exceeded the 3-month limit of §154(b)(2)(C)(ii); and (3) it failed to credit Petitioners for the 282 days between October 3, 2003 (the application filing date plus 3 years) and the grant of the '180 patent on July 13, 2004 (§154(b)(1)(B)(iii)).

Correction of the foregoing errors is requested in view of the facts, statutory provisions, and remarks that follow.

FACTS

The USPTO's calculation of 68 days of PTA for the '180 patent (a copy of the calculations from PAIR is attached as Exhibit 2) appears to be based on the following:

(1) A reduction of 46 days of PTA under 35 U.S.C. § 154(b)(2)(C)(ii) for any period of time in excess of 3 months that is taken to respond to a notice from the USPTO making any rejection, objection, argument or other request. A Notice to File Missing Parts of Nonprovisional Application was mailed on December 1, 2000. According to the USPTO's PTA calculations, Petitioners responded to the Notice on April 16, 2001. According to the USPTO's calculations, the PTA should be reduced by a period of 46 days for the time in excess of 3 months Petitioners took to file a response to the Notice. As shown by the USPTO date stamp on the response to the Notice to File Missing Parts of a Nonprovisional Application, Applicants responded on January 16, 2001, not April 16, 2001.

(2) An increased period of patent term of 86 days under 35 U.S.C. §154(b)(1)(A)(i) due to failure by the USPTO to mail an action under 35 U.S.C. § 132 not later than 14 months from the date on which an application was filed under 35 U.S.C. § 111(a) ("14 Month Delay"), which was on October 3, 2000. The first office action was mailed on February 27, 2002. Therefore, the '180 patent should be entitled to an increased period of patent term of 86 days (i.e., the period from December 3, 2001, 14 months from the filing date, until February 27, 2002) for this delay by the USPTO. The USPTO's calculations properly account for this USPTO delay.

(3) An additional increased period of patent term of 115 days under 35 U.S.C. §154(b)(1)(A)(ii) due to failure by the USPTO to respond to a reply under 35 U.S.C. § 132 not later than 4 months from the date on which the reply was filed. The reply at issue here was initially submitted on March 26, 2000 but was misplaced by the USPTO. Duplicates of this response were submitted to the USPTO on October 22, 2002 and October 23, 2003 by facsimile. A subsequent office action by the USPTO was mailed on November 18, 2002. Therefore, the '180 patent should be entitled to an additional 115 days of PTA (i.e., the period from July 26, 2002 until November 18, 2002) for this delay by the USPTO. Petitioners do not dispute this reduction.

(4) A reduction of 84 days of PTA under 35 U.S.C. § 154(b)(2)(C)(ii) for any period of time in excess of 3 months that is taken to respond to a notice from the USPTO making any rejection, objection, argument or other request. A Non-Final Office Action was mailed on November 18, 2002. A response to the Non-Final Office Action was filed on May 13, 2003. According to the USPTO's calculations, the PTA should be reduced by a period of 84 days for the time in excess of 3 months Petitioners took to respond to the Non-Final Office Action. Petitioners do not dispute this reduction.

(5) A reduction of 3 days of PTA under 35 U.S.C. § 154(b)(2)(C)(i) for any period of time the applicant failed to engage in reasonable efforts to conclude prosecution of the application. According to 37 C.F.R. §1.704(c)(8), submission of a supplemental reply, other than a supplemental reply expressly requested by the examiner, after a reply has been filed constitutes a failure of the applicant to engage in reasonable efforts to conclude examination. Therefore, the total amount of PTA should be reduced by the amount of time between the date an initial reply was filed and the date any supplemental reply was filed. An initial response to a

Non-Final Office Action was filed on May 13, 2003 and a supplemental response was filed on May 16, 2003. According to the USPTO's calculations, the PTA should be reduced by a period of 3 days for the period between the initial reply and the supplemental reply. Petitioners do not dispute this reduction.

According to the USPTO's calculations, the '180 patent is entitled to a total PTA of:

86 days + 115 days - 46 days - 84 days -3 days = 68 days.

The USPTO did not include any PTA under 35 U.S.C. § 154(b)(1)(B) due to the failure of the USPTO to issue a patent within 3 years after the actual filing date of the application in the United States.

The '180 patent is not subject to a terminal disclaimer.

APPLICABLE STATUTES

35 U.S.C. §154(b)(1) provides three "guarantees" to patent applicants and requires that they be compensated for various actions during prosecution that delay the timely issuance of a patent. The types of delays for which applicants are compensated by adjustments to patent term are set forth in subparagraphs (A), (B), and (C) of the statute and are referred to in this Petition as "A Delay," "B Delay," and "C Delay," respectively.

> (1) PATENT TERM GUARANTEES. –
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> > (A) GUARANTEE OF PROMPT PATENT AND TRADEMARK OFFICE RESPONSES. – Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to the failure of the Patent and Trademark Office to –
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> > > (i) provide at least one of the notifications under section 132 of this title or a notice of allowance under section 151 of this title not later than 14 months after –

(I) the date on which an application was filed under section 111(a) of this title; or

(II) the date of commencement of the national stage under section 371 in an international application;

(ii) respond to a reply under section 132, or to an appeal taken under section 134, within 4 months after the date on which the reply was filed or the appeal was taken;

(iii) act on an application within 4 months after the date of a decision by the Board of Patent Appeals and Interferences under section 134 or 135 or a decision by a Federal court under section 141, 145, or 146 in a case in which allowable claims remain in the application; or

(iv) issue a patent within 4 months after the date on which the issue fee was paid under section 151 and all outstanding requirements were satisfied,

the term of the patent shall be extended 1 day for each day after the end of the period specified in clause (i), (ii), (iii), or (iv), as the case may be, until the action described in such clause is taken.

(B) GUARANTEE OF NO MORE THAN 3-YEAR APPLICATION PENDENCY. – Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to the failure of the United States Patent and Trademark Office to issue a patent within 3 years after the actual filing date of the application under section 111(a) in the United States or, in the case of an international application, the date of commencement of the national stage under section 371 in the international application, not including –

(i) any time consumed by continued examination of the application requested by the applicant under section 132(b);

(ii) any time consumed by a proceeding under section 135(a), any time consumed by the imposition of an order under section 181, or any time consumed by appellate review by the Board of Patent Appeals and Inferences or by a Federal court; or

(iii) any delay in the processing of the application by the United States Patent and Trademark Office requested by the applicant except as permitted by paragraph (3)(C),

the term of the patent shall be extended 1 day for each day after the end of that 3-year period until the patent is issued.

(C) GUARANTEE OR ADJUSTMENTS FOR DELAYS DUE TO INTERFERENCES, SECRECY ORDERS, AND APPEALS. – Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to –

(i) a proceeding under section 135(a);

(ii) the imposition of an order under section 181; or

(iii) appellate review by the Board of Patent Appeals and Interferences or by a Federal court in a case in which the patent was issued under a decision in the review reversing an adverse determination of patentability,

the term of the patent shall be extended 1 day for each day of pendency of the proceeding, order, or review, as the case may be.

Countering these increases in patent term are the limitations set forth in 35 U.S.C. § 154(b)(2):

(2) LIMITATIONS. –

(A) IN GENERAL. – To the extent that periods of delay attributable to grounds specified in paragraph (1) overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed.

(B) DISCLAIMED TERM. – No patent the term of which has been disclaimed beyond a specified date may be adjusted under this section beyond the expiration date specified in the disclaimer.

(C) REDUCTION OF PERIOD OF ADJUSTMENT. –

(i) The period of adjustment of the term of a patent under paragraph (1) shall be reduced by a period equal to the period of time during which the applicant failed to engage in reasonable efforts to conclude prosecution of the application.

(ii) With respect to adjustments to patent term made under the authority of paragraph (1)(B), an applicant shall be deemed to have failed to engage in reasonable efforts to conclude

processing or examination of an application for the cumulative total of any periods of time in excess of 3 months that are taken to respond to a notice from the Office making any rejection, objection, argument, or other request, measuring such 3-month period from the date the notice was given or mailed to the applicant.

(iii) The Director shall prescribe regulations establishing the circumstances that constitute a failure of an applicant to engage in reasonable efforts to conclude processing or examination of an application.

REMARKS

I. The USPTO Made Three Errors in its PTA Calculation

A. The USPTO Improperly Charged Petitioners for 46 Days of Delay in Responding to a Notice to File Missing Parts

The USPTO mailed a Notice to File Missing Parts of a Nonprovisional Application ("Notice") on December 1, 2000. The USPTO's PTA calculations wrongly state that Petitioners responded to that Notice on April 16, 2001. According to the USPTO's calculations, the PTA should therefore be reduced by a period of 46 days for the time in excess of 3 months Petitioners took to file a response to the Notice.

This assessment of 46 days delay is incorrect. The response to the Notice is date stamped by the USPTO January 16, 2001 in the image file wrapper, clearly showing that the response was filed within the 3-month period permitted by 35 U.S.C. § 154(b)(2)(C)(ii). The USPTO's assumption of an April 16, 2001 filing date is simply wrong and the USPTO should have counted *no* days of delay for this filing.

B. The USPTO Failed to Account For an Untimely Response that Reduces the PTA to Which the Patent is Entitled

35 U.S.C. § 154(b)(2)(C)(ii) requires the PTA to be reduced by "any periods of time in excess of 3 months that are taken to respond to a notice from the Office making any rejection …"

The USPTO mailed a Final Office Action on June 13, 2003, to which Petitioners did not reply until December 8, 2003. The USPTO's PTA calculation overlooked that 86 day period of applicant delay by which the filing date of that response exceeded the 3-month limit of § 154(b)(2)(C)(ii).

C. The USPTO Failed to Credit Petitioners for 282 Days of B Delay

The application that eventually issued as the '180 patent was filed on October 3, 2000. The application was still pending on October 3, 2003 (i.e., 3 years after filing) and did not issue as a patent until July 13, 2004. Accordingly, under §154(b)(1)(B), Petitioners should have been credited with 282 days of B Delay for the period between October 3, 2003, and the patent's issuance on July 13, 2004.

Petitioners were not credited with this 282 day period of B Delay, however, because the USPTO's regulations then in effect (69 Fed. Reg. 21704 at 21706 (Apr. 24, 2004) ("2004 Notice")) incorrectly interpreted the language of 35 U.S.C. § 154(b)(2)(A) concerning "overlap" of A Delay and B Delay. The 2004 Notice interpreted the overlap of A Delay and B Delay to include any period of A Delay that accrued within the first three years after filing a patent application. The result of this interpretation was that the USPTO only granted PTAs amounting to the greater of A Delay or B Delay. As the USPTO is well aware, the Federal Circuit ruled that this method of calculating the overlap of A Delay and B Delay was erroneous. *Wyeth v. Kappos*, 591 F.3d 1364 (Fed. Cir. 2010). Rather, the *Wyeth* court held that in determining A Delay/B Delay overlap, the USPTO should have aggregated A Delay and B Delay except to the extent that such aggregation would result in counting the same calendar days twice. In view of *Wyeth*, the USPTO revised its policy to account for B Delay in this manner for patents issuing on or after March 2, 2010, and set up an Interim Procedure through which the owners of patents issued

from 180 days before February 1, 2010, through March 1, 2010, could have their PTAs corrected, provided the request for correction was filed within 180 days of the patent's issuance. 75 Fed. Reg. 5043 (Feb. 1, 2010).

In the interest of clarity, Petitioners separately discuss the two distinct phases that together create the 282 day period of B Delay for which they should have received credit.

1. October 3, 2003 (filing date plus 3 years) to December 8, 2003 (filing date of RCE)

It is indisputable that under current (i.e., post-*Wyeth*) USPTO policy, Petitioners are entitled to PTA credit for the 66 day period starting from the third anniversary of the application's filing to the subsequent filing of an RCE. As noted above, *Wyeth* held that in determining A Delay/B Delay overlap, the USPTO should have aggregated A Delay and B Delay except to the extent that such aggregation would result in counting the same calendar days twice. All of the A Delay for which the USPTO credited Petitioners in this case occurred *before* the third anniversary of the application's filing. Accordingly, the 66 days of B Delay between October 3, 2003 (filing date plus 3 years) and December 8, 2003 (filing of the RCE) did not overlap with the A Delay days under *Wyeth* and the USPTO should have added at least 66 days of B Delay to the total PTA as it now does following its post-*Wyeth* regulations.

2. December 8, 2003 (RCE filed) to July 13, 2004 (Issuance of Patent)

(a) Petitioners Are Entitled to PTA for the Entire 216 Day Period from RCE Filing to Patent Issuance

The USPTO failed to credit Petitioners for the 216 days of B Delay from the filing of the RCE on December 8, 2003, to the issuance of the patent on July 13, 2004. This exclusion is consistent with the current USPTO policy set forth in 37 C.F.R. §1.703(b), which provides that the PTA shall "not includ[e] . . . [t]he number of days . . . in the period beginning on the date on

which a request for continued examination of the application under 35 U.S.C. §132(b) was filed and ending on the date the patent was issued." However, as held by Judge Ellis in *Exelixis, Inc. v. Kappos*, No. 1:12-cv-00096-TSE-TCB (E.D. Va. Nov. 1, 2012, as amended Nov. 6, 2012) (attached as Exhibit 3), that policy is "not in accordance with law" and "in excess of [the USPTO's] statutory authority" to the extent it denies PTA for days consumed by RCEs that were filed *after* the three-year application to issuance deadline has passed. Slip. op. at 13, and 15 n.19; (reasoning adopted and followed by Judge Huvelle in *Novartis AG, et al., v. Kappos*, No. 1:10-cv-01138-ESH (D.D.C Nov. 15, 2012) attached as Exhibit 4, at 19-24).

35 U.S.C. § 154(b)(1)(B) provides, in relevant part:

> (B) GUARANTEE OF NO MORE THAN 3-YEAR APPLICATION PENDENCY. – Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to the failure of the United States Patent and Trademark Office to issue a patent within 3 years after the actual filing date of the application in the United States, not including –
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> (i) any time consumed by continued examination of the application requested by the applicant under section 132 (b);
>
> (ii) [not applicable here]; or
>
> (iii) [not applicable here],
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> the term of the patent shall be extended 1 day for each day after the end of that 3-year period until the patent is issued.

The above-quoted statutory language includes two distinct parts. The first relates to how the period of three years from filing is calculated and provides that any time consumed by the activities listed in subparagraphs (i), (ii), and (iii) does not count toward that three year period. Thus, if an applicant files an RCE less than three years after the application's filing date, the three-year clock is tolled until the continued examination is concluded. *Exelixis*, Slip op. at 11. The second part of the statute specifies the remedy provided to the applicant once the three-year

deadline is reached: "the term of the patent shall be extended 1 day for each day after the end of that 3-year period until the patent is issued." *Id.* at 11-12.

It is indisputable that the language "not including – (i) any time consumed by continued examination of the application requested by the applicant . . ." is part of and applies only to the first part of the statute, which defines how the three-year period is calculated. It is equally indisputable that the "not including" language does not modify the second part of the statute providing the remedy for inventors whose applications are still pending when the three-year deadline is reached. *Exelixis*, Slip. op. at 11 ("[T]he 'not including' portion of subparagraph (B), followed by (i), (ii), and (iii), clearly and umbiguously modifies and pertains to the three year period and does not apply to or refer to the day for day PTA remedy."). To the contrary, the remedy of 1 day of PTA for each day between the three-year deadline and the patent's issuance is limited only by paragraph (2).

The limitations of paragraph (2) do not include the filing of RCEs. Paragraph (2)(A) applies to overlap of delay periods under paragraph (1)(A), (B), and (C); paragraph (2)(B) applies to terminal disclaimers; and paragraph (2)(C) applies to delays due to the applicant's "fail[ure] to engage in reasonable efforts to conclude prosecution of the application." The filing of an RCE cannot constitute a failure to engage in reasonable efforts to conclude prosecution, and the UPTO has never contended that it has. In fact, 37 C.F.R. §1.704(c)(1)-(11) sets forth eleven types of delay that will be deducted from PTAs and conspicuously omits the filing and prosecution of RCEs. *Exelixis*, Slip op. at 13 (pointing out the inconsistency of the USPTO's

policy of penalizing applicants for filing RCEs when it comes to PTA calculations, but encouraging RCEs as a "valuable tool in the patent prosecution process" in other contexts).[1]

Under the plain terms of § 154(b)(1)(B) and (2), therefore, the filing of an RCE more than three years after the application's filing date has no effect on the PTA to which the applicant is entitled. *Exelixis*, Slip op. at 13 ("Put simply, RCE's have no impact on the PTA after the three year deadline has passed."). Rather, an RCE is relevant only if filed less than three years after the application's filing date, when it tolls the three-year clock of §154(b)(1)(B). *Id.* As

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[1] Shortly after the *Exelixis* decision discussed above (and the *Novartis* decision in the D.C. District Court, also referenced above), a different judge from the Eastern District of Virginia, Judge Brinkema, reached a contrary conclusion on this same issue, ruling that time consumed by RCEs filed after the three-year deadline should not be included in PTAs. *Exelixis, Inc. v. Kappos*, No. 1:12cv574 (LMB/TRS) (E.D. Va. Jan. 28, 2013) ("*Exelixis II*") (Exhibit 5 hereto). With due respect to Judge Brinkema, however, *Exelixis II* is not persuasive. *Exelixis II* starts from the premise that §154(b)(1)(B) is "silent" on the effect of RCEs filed after the three-year date. But neither Judge Ellis nor this Petition (nor Judge Huvelle in *Novartis*) relies on any alleged "silence" concerning RCEs. Rather, both Judge Ellis and Petitioners point out that Congress enacted a detailed statute providing that RCEs filed before the three-year date toll the three-year clock, but chose not to penalize applicants for RCEs filed after the three-year date. *See* §154(b)(2)(C) (setting forth activities that will be deducted from PTAs, but failing to list RCEs among them). Moreover, the USPTO's own regulations spell out eleven types of delay that will be deducted from PTAs and the prosecution of RCEs is not included. 37 C.F.R. §1.704(c)(1)-(11). Under these circumstances, the statute is clear and the construction process stops. *Exelixis*, Slip. op. at 10-15.

The rest of *Exelixis II* is devoted to showing that the USPTO's construction of the statute better effectuates the policy goals from the legislative history (an issue on which Judge Ellis reached the opposite conclusion), Slip. op. at 17-21, that Judge Ellis's construction could lead to "absurd results," Slip. op. at 21, and that the USPTO's construction leads to a more equitable result under the particular facts of *Exelixis II*, Slip. op. at 23-24. All of those considerations, however, are irrelevant since the statute simply is not written the way the USPTO and the *Exelixis II* court would like it to be. *See Exelixis*, Slip. op. at 14 ("Neither courts nor agencies may change . . . the plain language and meaning of a statute because of a belief, however well founded, that the statute would be improved thereby."), citing *Badaracco v. Comm'r of Internal Revenue*, 464 U.S. 386, 398 (1984) ("Courts are not authorized to rewrite a statute because they might deem its effects susceptible of improvement."); *see also Wyeth v. Kappos*, 591 F.3d 1364, 1370-71 (Fed. Cir. 2010) ("[T]he law has put a policy in effect that [the] court must enforce, not criticize or correct."). Since *Exelixis II* construes §154(b)(1)(B) in a way that conflicts with the plain meaning of the statute, the Office should not follow it in deciding this petition.

noted previously, the RCE at issue here was filed over two months after the three-year deadline had passed. The USPTO's failure to credit Petitioners for the 216 days of B Delay from the RCE filing on December 8, 2003 to the issuance of the patent on July 13, 2004 was therefore erroneous and should be corrected. *Id.* at 16 (where RCE filed after 3 year date, applicant entitled to PTA for entire time from RCE filing to patent issuance).

(b) At the Very Least, Petitioners Are Entitled to PTA Credit for the 125 Day Period From the Notice of Allowance to the Issuance of the Patent

As shown above, and as held by the court in the *Exelixis* case, RCEs filed more than three years after the filing of the underlying patent application are irrelevant to PTA calculations. Thus, the entire time from the filing of the RCE on December 8, 2003 to the '180 patent's issuance on July 13, 2004 should have been included in the PTA. Petitioners here separately address the period between notice of allowance and issuance, however, because even if (contrary to the statute) the time under continued examination is excluded from the PTA, there is no statutory basis for excluding the days between the notice of allowance and the patent's issuance. To the contrary, even if subparagraph (i) of § 154(b)(1)(B) applied to the remedy provision of the three years to issuance guarantee, it would not exclude the time between notice of allowance and issuance because it addresses only the time "consumed by continued examination." By excluding the *entire* time from RCE filing to patent issuance from the B Delay period, 37 C.F.R. §1.703(b)(1) contravenes this statutory limitation.

The only time "consumed by continued examination" is the time between the filing of an RCE and the notice of allowance. "Examination" of a patent application involves the examiner's search and review of prior art, consideration of application content and disclosures, and rejection of any claims that fail to comply with the statutory requirements. *See generally* MPEP, ch. 700,

"Examination of Applications." Once an examiner determines that the "applicant is entitled to a patent under the law, a written notice of allowance shall be given or mailed to the applicant." 35 U.S.C. § 151. Thus, once the notice of allowance is mailed, prosecution is closed and "examination" ends. *Id.*; *see* also Department of Commerce, Patent and Trademark Office, Changes to Patent Practice and Procedure, 62 Fed. Reg. 53, 132, 53, 145 (Oct. 10, 1997) ("Upon mailing of a notice of allowance under § 1.311, prosecution of an application before the Office is concluded."); *see*, *e.g.,* Notice of Allowance of Application No. 09/678,682 (mailed March 10, 2004) **("THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.")** (emphasis in original).

When prosecution of the application on the merits has concluded, there can no longer be any "continued examination" of that application by the USPTO. Accordingly, the mailing of a notice of allowance must be the end point of the "continued examination" period under the statute. The time consumed by the ministerial steps taken by the USPTO to process and print a patent after allowance is not "time consumed by continued examination" and cannot be excluded from the accrual of B Delay under §154(b)(1)(B). The USPTO's refusal to acknowledge the accrual of B Delay after the date of the notice of allowance is an improper deprivation of patent term.

Moreover, the statutory phrase "time consumed by continued examination of the application requested by the applicant" necessarily encompasses only delays the RCE *caused* in some manner. The filing of an RCE has no effect on the time between the notice of allowance and the issuance of a patent. In other words, the time between the notice of allowance of the patent application at issue here and the grant of the patent would have elapsed regardless of

whether an RCE had been filed. This is yet another reason why the time between notice of allowance and issuance was not "consumed" by the RCE and therefore should not have been excluded from the PTA.[2]

II. The Correct PTA to Which Petitioners Are Entitled Is 310 Days

Under the proper construction of §154(b) discussed above, the correct PTA to which the '180 patent is entitled is as follows:

35 U.S.C. §154(b)(1)(A)

(1) Plus 86 days for the period from December 3, 2001 (i.e., 14 months from the October 3, 2000, filing date of the application) to February 27, 2002, when the USPTO mailed the first office action.

(2) Plus 115 days for the period from July 26, 2000 (i.e., 4 months after the March 26, 2000, filing of applicants' reply under 35 U.S.C. §132) to November 18, 2002, when the USPTO mailed the next office action.

Total PTA under 35 U.S.C. §154(b)(1)(A) = 201 days

35 U.S.C. §154(b)(1)(B)

Plus 282 days for the period from October 3, 2003 (3 years after the October 3, 2000, filing date of the patent application) to the grant of the '180 patent on July 13, 2004.

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[2] While the *Exelixis* and *Novartis* courts did not specifically reach this issue in view of the finding that the entire period after a post-three year RCE constitutes B Delay, Judge Brinkema in *Exelixis II* has taken the opposite view. Slip. Op. at 24-27. Petitioners respectfully disagree with the *Exelixis II* analysis that the post-allowance period represents continued examination and delay caused by the filing of the RCE. In fact, the delay between the notice of allowance and patent issuance occurs any time an application is allowed, regardless of whether an RCE had been filed, or not. And, as discussed above, the USPTO states in the notice of allowance itself that the application **has been examined** and that **prosecution on the merits is closed** -- expressly stating that the examination period is over. This holding is contrary to the statute and, thus, should the USPTO reach this issue, the USPTO should not follow this reasoning.

This 282 day B Delay period comprises the following time periods:

- 66 days for the period from October 3, 2003 (3 years after the October 3, 2000, filing date of the patent application) to December 8, 2003, when applicants filed a request for continuing examination (RCE).
- 216 days for the period from December 8, 2003 (the filing of the RCE) to July 13, 2004, when the patent was granted.

TOTAL PTA under §154(b)(1)(B) = 282 days.

35 U.S.C. §154(b)(2)(A)

There is no overlap between the PTA days accumulated under §154(b)(2)(A) and the PTA days accumulated under §154(b)(1)(B). Accordingly, there is no reduction in PTA under §154(b)(2)(A).

35 U.S.C. §154(b)(2)(C) correction

(1) Minus 84 days for the period from February 18, 2003 (3 months after the mailing of a non-final office action on November 18, 2002) to May 13, 2003, when Petitioners responded to that office action.

(2) Minus 3 days for the period from May 13, 2003, when Petitioners filed a response to the non-final office action of November 18, 2002, to May 16, 2003, when Petitioners filed a supplemental response to that office action.

(3) Minus 86 days for the period from September 13, 2003 (3 months after the mailing of a final office action on June 13, 2003) to December 8, 2003, when a response to that office action and an RCE were filed.

TOTAL §154(b)(2)(C) correction = minus 173 days.

Accordingly, the correct PTA of the '180 patent is 201 days (A Delay) + 282 days (B Delay) - 173 days (C Correction) = 310 days.

CONCLUSION

For the foregoing reasons, Petitioners respectfully submit that their request for reconsideration of the PTA for the '180 patent should be GRANTED and the PTA should properly be indicated as 310 days. Early notification of such action is earnestly solicited.

In accordance with 37 C.F.R. §1.704(b) and (d), Petitioners submit herewith the requisite fee under 37 C.F.R. §1.19(e). In the event that the Office determines that additional fees are required, it is requested that any underpayment be charged to their undersigned Representatives' deposit account (Deposit Account No. 02-2955). Also submitted herewith is a Petition Under 37 C.F.R. §1.183 to permit the filing of this request for PTA recalculation outside the time prescribed by 37 C.F.R. §1.705(d).

Dated: April 8, 2013

Respectfully submitted,

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EXHIBIT 1

US006762180B1

(12) **United States Patent**
Roth et al.

(10) **Patent No.: US 6,762,180 B1**
(45) **Date of Patent: Jul. 13, 2004**

(54) **SUBSTITUTED INDOLINES WHICH INHIBIT RECEPTOR TYROSINE KINASES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 68 days.

(21) Appl. No.: **09/678,682**

(22) Filed: **Oct. 3, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/160,547, filed on Oct. 20, 1999.

(30) **Foreign Application Priority Data**

Oct. 13, 1999 (DE) 199 49 208
Aug. 31, 2000 (DE) 100 42 696

(51) **Int. Cl.**[7] **C07D 209/34**; C07D 401/12; C07D 403/12; C07D 405/12; A61K 31/404

(52) **U.S. Cl.** **514/228.2**; 544/373; 544/144; 544/58.2; 514/254.09; 514/323; 514/418; 514/235.2; 514/414; 546/201; 548/486; 548/467

(58) **Field of Search** 544/373, 144, 544/58.2; 514/254.09, 418, 235.2, 228.2, 414, 323; 546/201; 548/486, 467

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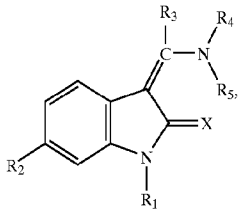
(57) **ABSTRACT**

Indolinones of the formula

(I)



having an inhibitory effect on receptor tyrosine kinases and cyclin/CDK complexes, as well as on the proliferation of endothelial cells and various tumor cells. Exemplary are:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(b) 3-Z-[(1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone, and

(c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-metboxycarbonyl-2-indolinone.

8 Claims, No Drawings

SUBSTITUTED INDOLINES WHICH INHIBIT RECEPTOR TYROSINE KINASES

RELATED APPLICATIONS

Benefit of U.S. Provisional Application Serial No. 60/160,547, filed on Oct. 20, 1999, is hereby claimed.

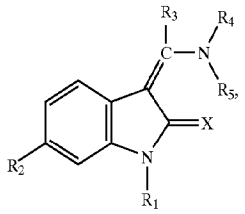
FIELD OF THE INVENTION

The present invention relates to novel indolinones that inhibit receptor tyrosine kinases, their use as pharmaceuticals, particularly in the treatment of proliferative diseases, and pharmaceutical compositions comprising these compounds.

DESCRIPTION OF THE INVENTION

The present invention provides new indolinones of general formula

(I)



substituted in the 6 position, the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof which have valuable properties.

The above compounds of general formula I wherein R_1 denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, in particular an inhibiting effect on various kinases, especially receptor tyrosine kinases such as VEGFR2, PDGFRα, PDGFRβ, FGFR1, FGFR3, EGFR, HER2, IGF1R and HGFR, as well as complexes of CDK's (Cyclin Dependent Kinases) such as CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8 and CDK9 with their specific cyclins (A, B1, B2, C, D1, D2, D3, E, F, G1, G2, H, I and K) and to viral cyclin (cf. L. Mengtao in J. Virology 71(3), 1984–1991 (1997)), and on the proliferation of cultivated human cells, in particular endothelial cells, e.g. in angiogenesis, but also on the proliferation of other cells, in particular tumour cells.

The other compounds of the above general formula I wherein R_1 does not denote a hydrogen atom or a prodrug group are valuable intermediate products for preparing the abovementioned compounds.

The present invention thus relates to the above compounds of general formula I, whereby those compounds wherein R_1 denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, pharmaceutical compositions containing the pharmacologically active compounds, the use thereof and processes for preparing them.

In the above general formula I

X denotes an oxygen or sulphur atom,

R_1 denotes a hydrogen atom or a prodrug group such as a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a carboxy group, a straight-chain or branched C_{1-6}-alkoxy-carbonyl group, a C_{4-7}-cycloalkoxy-carbonyl or an aryloxycarbonyl group,

a straight-chain or branched C_{1-6}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a

phenyl, heteroaryl, carboxy, C_{1-3}-alkoxy-carbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a straight-chain or branched C_{2-6}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom or a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group or, if R_4 does not denote an aminosulphonyl-phenyl or N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl-phenyl group, it may also denote a di-(C_{1-2}-alkyl)-aminocarbonyl group,

R_3 denotes a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl or heteroaryl group,

a phenyl or naphthyl group, a phenyl or naphthyl group mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group, whilst in the event of disubstitution the substituents may be identical or different and wherein the abovementioned unsubstituted as well as the mono- and disubstituted phenyl and naphthyl groups may additionally be substituted

by a hydroxy, hydroxy-C_{1-3}-alkyl or C_{1-3}-alkoxy-C_{1-3}-alkyl group,

by a cyano, carboxy, carboxy-C_{1-3}-alkyl, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

by a nitro group,

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino or amino-C_{1-3}-alkyl group,

by a C_{1-3}-alkylcarbonylamino, N—(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl, N—(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl, C_{1-3}-alkyl-sulphonylamino,

C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl, N—(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl or aryl-C_{1-3}-alkylsulphonylamino group,

by a cycloalkylamino, cycloalkyleneimino, cycloalkyleneiminocarbonyl, cycloalkyleneimino-C_{1-3}-alkyl, cycloalkyleneiminocarbonyl-C_{1-3}-alkyl or cycloalkyleneiminosulphonyl-C_{1-3}-alkyl group having 4 to 7 ring members in each case, whilst in each case the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH or —N(C_{1-3}-alkyl) group,

or by a heteroaryl or heteroaryl-C_{1-3}-alkyl group,

R_4 denotes a C_{3-7}-cycloalkyl group,

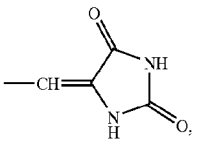
whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group,

or a phenyl group substituted by the group R_6, which may additionally be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-5}-alkyl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, amino, acetylamino, C_{1-3}-alkyl-sulphonylamnino, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl, di-(C_{1-3}-alkyl)-aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different and wherein

R_6 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

a cyano, nitro, amino, C_{1-5}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or heteroaryl group,

the group of formula



wherein the hydrogen atoms bound to a nitrogen atom may in each case be replaced independently of one another by a C_{1-3}-alkyl group,

a C_{1-3}-alkoxy group, a C_{1-3}-alkoxy-C_{1-3}-alkoxy, phenyl-C_{1-3}-alkoxy, amino-C_{2-3}-alkoxy, C_{1-3}-alkylamino-C_{2-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{2-3}-alkoxy, phenyl-C_{1-3}-alkylamino-C_{2-3}-alkoxy, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino-C_{2-3}-alkoxy, C_{5-7}-cycloalkyleneimino-C_{2-3}-alkoxy or C_{1-3}-alkylmercapto group,

a carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl, phenyl-C_{1-3}-alkylamino-carbonyl, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino-carbonyl, piperazinocarbonyl or N—(C_{1-3}-alkyl)-piperazinocarbonyl group,

a C_{1-3}-alkylaminocarbonyl or N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl group wherein an alkyl moiety is substituted by a carboxy or C_{1-3}-alkoxycarbonyl group or in the 2 or 3 position by a di-(C_{1-3}-alkyl)amino, piperazino, N—(C_{1-3}-alkyl)-piperazino or a 4- to 7-membered cycloalkyleneimino group,

a C_{3-7}-cycloalkyl-carbonyl group,

wherein the methylene group in the 4 position of the 6- or 7-membered cycloalkyl moiety may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group,

a 4- to 7-membered cycloalkyleneimino group wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused to a phenyl ring or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group,

a C_{1-4}-alkyl group substituted by the group R_7, wherein

R_7 denotes a C_{3-7}-cycloalkyl group,

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group or

in a 5- to 7-membered cycloalkyl group a —$(CH_2)_2$ group may be replaced by a —CO—NH group, a —$(CH_2)_3$ group may be replaced by a —NH—CO—NH or —CO—NH—CO group or a —$(CH_2)_4$ group may be replaced by a —NH—CO—NH—CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl group,

an aryl or heteroaryl group,

a hydroxy or C_{1-3}-alkoxy group,

an amino, C_{1-7}-alkylamino, di-(C_{1-7}-alkyl)-amino, phenylamino, N-phenyl-C_{1-3}-alkyl-amino, phenyl-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

an ω-hydroxy-C_{2-3}-alkyl-amino, N—(C_{1-3}-alkyl)-ω-hydroxy-C_{2-3}-alkyl-amino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino, di-(ω-(C_{1-3}-alkoxy)-C_{2-3}-alkyl)-amino or N-(dioxolan-2-yl)-C_{1-3}-alkyl-amino group,

a C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a C_{1-3}-alkylsulphonylamino, N—(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino, C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a hydroxycarbonyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-hydroxycarbonyl-C_{1-3}-alkyl-amino group,

a guanidino group wherein one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group,

a group of formula

$$—N(R_8)—CO—(CH_2)_n—R_9 \quad (II),$$

wherein

R_8 denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R_9 denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino, N—(C_{1-4}-alkyl)-phenylamino, benzylamino, N—(C_{1-4}-alkyl)-benzylamino or C_{1-4}-alkoxy group, a 4- to 7-membered cycloalkyleneimino group, whilst in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula

$$—N(R_{10})—(CH_2)_m—(CO)_o—R_{11} \quad (III),$$

wherein

R^{10} denotes a hydrogen atom, a C_{1-3}-alkyl group, a C_{1-3}-alkylcarbonyl, arylcarbonyl, phenyl-C_{1-3}-alkyl-carbonyl, C_{1-3}-alkylsulphonyl, arylsulphonyl or phenyl-C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2, 3 or 4,

o denotes the number 1 or, if m denotes one of the numbers 2, 3 or 4, o may also denote the number 0 and

R_{11} denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino, N—(C_{1-4}-alkyl)-phenylamino, benzylamino, N—(C_{1-4}-alkyl)-benzylamino, C_{1-4}-alkoxy or C_{1-3}-alkoxy-C_{1-3}-alkoxy group, a di-(C_{1-4}-alkyl)-amino-C_{1-3}-alkylamino group optionally substituted in the 1 position by a C_{1-3}-alkyl group or a 4- to 7-membered cycloalkyleneimino group, wherein

the cycloalkylene moiety may be fused to a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkylcarbonyl) or —N(benzoyl) group,

a C_{4-7}-cycloalkylamino, C_{4-7}-cycloalkyl-C_{1-3}-alkylamino or C_{4-7}-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond and wherein the abovementioned groups may each additionally be substituted at the amino-nitrogen atom by a C_{5-7}-cycloalkyl, C_{2-4}-alkenyl or C_{1-4}-alkyl group,

a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a nitro, C_{1-3}-alkyl, C_{1-3}-alkoxy or amino group, and/or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and/or

the methylene group in the 3 position of a 5-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy or C_{1-3}-alkoxy-C_{1-3}-alkyl group,

the methylene group in the 3 or 4 position of a 6- or 7-membered cycloalkyleneimino group may in each case be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkoxy-C_{1-3}-alkyl, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkyl-amino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl-), —N(phenyl), —N(phenyl-C_{1-3}-alkyl-), —N(C_{1-3}-alkyl-carbonyl-), —N(C_{1-4}-hydroxy-carbonyl-), —N(C_{1-4}-alkoxy-carbonyl-), —N(benzoyl-) or —N(phenyl-C_{1-3}-alkyl-carbonyl-) group,

wherein a methylene group linked to an imino-nitrogen atom of the cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl group or in a 5- to 7-membered monocyclic cycloalkyleneimino group or a cycloalkyleneimino group fused to a phenyl group the two methylene groups linked to the imino-nitrogen atom may each be replaced by a carbonyl group,

or R_6 denotes a C_{1-4}-alkyl group which is substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

an N—(C_{1-3}-alkyl)-C_{2-4}-alkanoylamino group) which is additionally substituted in the alkyl moiety by a carboxy or C_{1-3}-alkoxycarbonyl group,

a group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein

R_{12} denotes a hydrogen atom, a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group or a C_{1-3}-alkyl group terminally substituted by a phenyl, heteroaryl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, aminocarbonyl, C_{1-4}-alkylamino-carbonyl, di-(C_{1-4}-alkyl)-amino-carbonyl, C_{1-3}-alkyl-carbonyl, C_{1-3}-alkyl-sulphonylamino,

N—(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino, C_{1-3}-alkyl-aminosulphonyl or di-(C_{1-3}-alkyl)-aminosulphonyl group and

p denotes one of the numbers 0, 1, 2 or 3 and

R_{13} assumes the meanings of the abovementioned group R_7, or, if p denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula

$$—N(R_{14})—(CH_2)_q—(CO)_r—R_{15} \quad (V),$$

wherein

R_{14} denotes a hydrogen atom, a C_{1-4}-alkyl group, a C_{1-3}-alkylcarbonyl, arylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, heteroarylcarbonyl, heteroaryl-C_{1-3}-alkylcarbonyl, C_{1-4}-alkylsulphonyl, arylsulphonyl, phenyl-C_{1-3}-alkylsulphonyl, heteroarylsulphonyl or heteroaryl-C_{1-3}-alkyl-sulphonyl group,

q denotes one of the numbers 1, 2, 3 or 4,

r denotes the number 1 or, if q is one of the numbers 2, 3 or 4, it may also denote the number 0 and

R_{15} assumes the meanings of the abovementioned group R_7,

a group of formula

$$—N(R_{16})—SO_2—R_{17} \quad (VI),$$

wherein

R_{16} denotes a hydrogen atom or a C_{1-4}-alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or N—(C_{1-3}-alkyl)-trifluoromethyl-carbonyl-amino group and

R_{17} denotes a C_{1-3}-alkyl group,

an amino group substituted by a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-carbonyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-sulphonyl group and a di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyl group,

or an N—(C_{1-3}-alkyl)-C_{1-5}-alkylsulphonylamino or N—(C_{1-3}-alkyl)-phenylsulphonylamino group wherein the alkyl moiety is additionally substituted by a cyano or carboxy group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R_6 may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-5}-alkyl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylamino-carbonyl, di-(C_{1-4}-alkyl)-amino-carbonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl, di-(C_{1-3}-alkyl)-aminosulphonyl, C_{1-3}-alkyl-sulphonylamino, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group,

and

R_5 denotes a hydrogen atom or a C_{1-3}-alkyl group,

wherein by an aryl group is meant a phenyl or naphthyl group optionally mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, trifluoromethyl, nitro, carboxy, aminocarbonyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group and

by a heteroaryl group is meant a monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C_{1-3}-alkyl group in the carbon skeleton, wherein

the 6-membered heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally substituted by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group, an oxygen or sulphur atom or

an imino group optionally substituted by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group or an oxygen or sulphur atom and additionally a nitrogen atom or

an imino group optionally substituted by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group and two nitrogen atoms,

and moreover a phenyl ring may be fused to the abovementioned monocyclic heterocyclic groups via two adjacent carbon atoms and the bonding takes place via a nitrogen atom or via a carbon atom of the heterocyclic moiety or a fused phenyl ring,

some or all of the hydrogen atoms in the abovementioned alkyl and alkoxy groups or in the alkyl moieties contained in the above-defined groups of formula I optionally being replaced by fluorine atoms,

the saturated alkyl and alkoxy moieties with more than 2 carbon atoms which are present in the groups defined hereinbefore also include the branched isomers thereof, such as for example the isopropyl, tert.butyl, isobutyl group, unless otherwise stated, and

additionally the hydrogen atom of any carboxy group present or a hydrogen atom bound to a nitrogen atom, e.g. a hydrogen atom of an amino, alkylamino or imino group or a saturated N-heterocycle such as the piperidinyl group, may each be replaced by a group which can be cleaved in vivo.

By a group which can be cleaved in vivo from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C_{1-6}-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or $R_eCO—O—(R_fCR_g)—O—CO$ group wherein

R_e denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_f denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C_{1-3}-alkyl or $R_eCO—O—(R_fCR_g)—O$ group wherein R_e to R_g are as hereinbefore defined,

wherein additionally the amino group may be a phthalimido group, whilst the abovementioned ester groups may also be used as a group which can be converted in vivo into a carboxy group.

One sub-group of compounds of general formula I which deserves special mention comprises those wherein

X, R_1 and R_3 to R_5 are as hereinbefore defined and

R_2 denotes a straight-chain or branched C_{1-6}-alkoxy-carbonyl group, a C_{4-7}-cycloalkoxycarbonyl or a aryloxycarbonyl group,

a straight-chain or branched C_{1-6}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a straight-chain or branched C_{2-6}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom or a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

A second sub-group of compounds of general formula I which deserves special mention comprises those wherein

X, R_1 and R_3 to R_5 are as hereinbefore defined and

R_2 denotes an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group or, if R_4 does not denote an aminosulphonyl-phenyl or N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl-phenyl group, R_2 may also denote a di-(C_{1-2}-alkyl)-aminocarbonyl group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

A third sub-group of compounds of general formula I which deserves special mention comprises those wherein

X, R_1 to R_3 and R_5 are as hereinbefore defined and

R_4 denotes an R_7—(C_{1-4}-alkyl)-phenyl group, wherein

R_7 denotes an amino, C_{1-7}-alkylamino, di-(C_{1-7}-alkyl)-amino, phenylamino, N-phenyl-C_{1-3}-alkyl-amino, phenyl-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

or a phenyl group substituted by the group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein R_{12}, p and R_{13} are as hereinbefore defined,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

Preferred compounds of general formula I are those wherein

R_1 and R_3 are as hereinbefore defined and

X denotes an oxygen atom,

R_2 denotes a carboxy group, a straight-chain or branched C_{1-6}-alkoxy-carbonyl group, a C_{5-7}-cycloalkoxycarbonyl or a phenoxycarbonyl group,

a straight-chain or branched C_{1-3}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a straight-chain or branched C_{2-3}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom, by a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group or, if R_4 does not denote an aminosulphonyl-phenyl or N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl-phenyl group, it may also denote a di-(C_{1-2}-alkyl)-aminocarbonyl group,

R_4 denotes a C_{3-7}-cycloalkyl group,

whilst the methylene group in the 4 position of a 6 or 7-membered cycloalkyl group may be substituted by

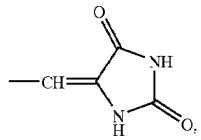
an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group,

or a phenyl group substituted by the group R_6, which may additionally be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C_{1-3}-alkyl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, amino, acetylamino, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, nitro or cyano groups, wherein the substituents may be identical or different and wherein

R_6 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

a cyano, nitro, amino, C_{1-5}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or heteroaryl group,

the group of formula



wherein a hydrogen atom bound to the nitrogen atom may be replaced by a C_{1-3}-alkyl group,

a C_{1-3}-alkoxy group, an amino-C_{2-3}-alkoxy, C_{1-3}-alkylamino-C_{2-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{2-3}-alkoxy, phenyl-C_{1-3}-alkylamino-C_{2-3}-alkoxy, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino-C_{2-3}-alkoxy, pyrrolidino-C_{2-3}-alkoxy, piperidino-C_{2-3}-alkoxy or C_{1-3}-alkylmercapto group,

a carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, phenyl-C_{1-3}-alkylamino-carbonyl or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino-carbonyl group,

a C_{3-7}-cycloalkyl-carbonyl group,

wherein the methylene group in the 4 position of the 6- or 7-membered cycloalkyl moiety may be replaced by an —NH or —N(C_{1-3}-alkyl) group,

a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH or —N(C_{1-3}-alkyl) group,

a C_{1-4}-alkyl group terminally substituted by the group R_7, wherein

R_7 denotes a C_{5-7}-cycloalkyl group,

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an —NH or —N(C_{1-3}-alkyl) group or

in a 5- to 7-membered cycloalkyl group a —$(CH_2)_2$ group may be replaced by a —CO—NH group, a —$(CH_2)_3$ group may be replaced by a —NH—CO—NH— or a —$(CH_2)_4$ group may be replaced by a —NH—CO—NH—CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl group,

a phenyl or heteroaryl group,

a hydroxy or C_{1-3}-alkoxy group,

an amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)-amino, phenylamino, N-phenyl-C_{1-3}-alkylamino, phenyl-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

a ω-hydroxy-C_{2-3}-alkyl-amino, N—(C_{1-3}-alkyl)-ω-hydroxy-C_{2-3}-alkyl-amino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino, di-(ω-(C_{1-3}-alkoxy)-C_{2-3}-alkyl)-amino or N—(dioxolan-2-yl)-C_{1-3}-alkyl-amino group,

a C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a C_{1-3}-alkylsulphonylamino, N—(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino, C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)amino group,

a hydroxycarbonyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-hydroxycarbonyl-C_{1-3}-alkyl-amino group

a guanidino group wherein a hydrogen atom may be replaced by a C_{1-3}-alkyl group,

a group of formula

$$—N(R_8)—CO—(CH_2)_n—R_9 \quad (II),$$

wherein

R_8 denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R_9 denotes an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenylamino, benzylamino or C_{1-4}-alkoxy group, a 5- to 7-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula

$$—N(R_{10})—(CH_2)_m—(CO)_o—R_{11} \quad (III),$$

wherein

R_{10} denotes a hydrogen atom, a C_{1-3}-alkyl group, a C_{1-3}-alkylcarbonyl or C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2 or 3,

o denotes the number 1 or, if m is one of the numbers 2 or 3, o may also denote the number 0 and

R_{11} denotes an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-4}-alkoxy or C_{1-3}-alkoxy-C_{1-3}-alkoxy group or a 5- to 7-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group,

a C_{4-7}-cycloalkylamino or C_{4-7}cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond,

a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl group or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group and/or

the methylene group in position 3 of the pyrrolidino group may be substituted by a hydroxy or C_{1-3}-alkoxy group,

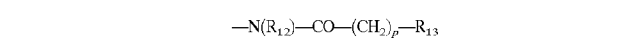
in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(phenyl-C_{1-3}-alkyl), —N(C_{1-3}-alkyl-carbonyl), —N(C_{1-4}-alkoxy-carbonyl), —N(benzoyl) or —N(phenyl-C_{1-3}-alkyl-carbonyl) group,

wherein a methylene group linked to an imino-nitrogen atom of the cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl group or in a 5- to 6-membered monocyclic cycloalkyleneimino group or a cycloalkyleneimino group fused to a phenyl group the two methylene groups linked to the imino-nitrogen atom may each be replaced by a carbonyl group,

or R_6 denotes a C_{1-4}-alkyl group which is terminally substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

a group of formula



$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

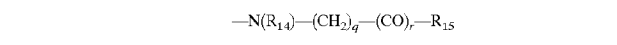
wherein

R_{12} denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl group and

p denotes one of the numbers 0, 1, 2 or 3 and

R_{13} assumes the meanings of the abovementioned group R_7, or, if p denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula



$$—N(R_{14})—(CH_2)_q—(CO)_r—R_{15} \quad (V),$$

wherein

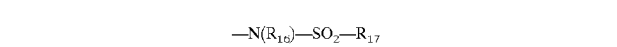
R_{14} denotes a hydrogen atom, a C_{1-4}-alkyl group, a C_{1-3}-alkylcarbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, heteroarylcarbonyl, heteroaryl-C_{1-3}-alkylcarbonyl, C_{1-4}-alkylsulphonyl, phenylsulphonyl, phenyl-C_{1-3}-alkylsulphonyl- heteroarylsulphonyl or heteroaryl-C_{1-3}-alkyl-sulphonyl group,

q denotes one of the numbers 1, 2, 3 or 4,

r denotes the number 1 or, if q is one of the numbers 2, 3 or 4, it may also denote the number 0 and

R_{15} assumes the meanings of the abovementioned group R_7,

a group of formula



$$—N(R_{16})—SO_2—R_{17} \quad (VI),$$

wherein

R_{16} denotes a hydrogen atom or a C_{1-4}-alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or N—(C_{1-3}-alkyl)-trifluoromethyl-carbonyl-amino group and

R_{17} denotes a C_{1-3}-alkyl group,

an amino group substituted by a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-carbonyl or di-(C_{1-3}-amino-C_{1-3}-alkyl-sulphonyl group and a di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyl group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R_6 may be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C_{1-3}-alkyl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group, and

R_5 denotes a hydrogen atom or a C_{1-3}-alkyl group,

whilst by a heteroaryl group as mentioned above is meant a pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, pyrazolyl, imidazolyl or triazolyl group optionally substituted in the carbon skeleton by a C_{1-3}-alkyl group wherein a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group and wherein the 5-membered heteroaryl groups containing at least one imino group are bound via a carbon or nitrogen atom,

a hydrogen atom bound to a nitrogen atom in the abovementioned groups may be replaced by a group which can be cleaved in vivo, particularly by an acetyl or tert.butoxycarbonyl group,

the carboxy groups contained in the abovementioned groups may each be substituted by a group which can be cleaved in vivo and may occur, for example, in the form of the tert.butoxycarbonyl group,

some or all of the hydrogen atoms in the abovementioned alkyl and alkoxy groups or in the alkyl moieties contained in the above-defined groups of formula I optionally being replaced by fluorine atoms and

the saturated alkyl and alkoxy moieties contained in the abovementioned groups, which contain more than 2 carbon atoms, may be straight-chain or branched, unless otherwise stated,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

One subgroup of preferred compounds of general formula I deserving special mention comprises those wherein

X, R_1 and R_3 to R_5 are as hereinbefore defined and

R_2 denotes a straight-chain or branched C_{1-6}alkoxy-carbonyl group, a C_{5-7}-cycloalkoxycarbonyl or a phenoxycarbonyl group,

a straight-chain or branched C_{1-3}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl-carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a straight-chain or branched C_{2-3}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

A second sub-group of preferred compounds of general formula 1 deserving special mention comprises those wherein

X, R_1 and R_3 to R_5 are as hereinbefore defined and

R_2 denotes an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group or, if R_4 does not denote an aminosulphonyl-phenyl or N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl-phenyl group, R_2 may also denote a di-(C_{1-2}-alkyl)-aminocarbonyl group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

A third sub-group of preferred compounds of general formula I deserving special mention comprises those wherein

X, R_1 to R_3 and R_5 are as hereinbefore defined and

R_4 denotes an R_7-(n-C_{1-4}-alkyl)-phenyl group, wherein

R_7 denotes an amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)-amino, phenylamino, N-phenyl-C_{1-3}-alkyl-amino, phenyl-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

or a phenyl group substituted by the group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein R_{12}, p and R_{13} are as hereinbefore defined,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

Particularly preferred compounds of general formula I are those wherein

X denotes an oxygen atom,

R_1 denotes a hydrogen atom,

R_2 denotes a carboxy group, a straight-chain or branched C_{1-4}-alkoxycarbonyl group or a phenoxycarbonyl group,

a straight-chain or branched C_{1-3}-alkoxycarbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a straight-chain or branched C_{2-3}-alkoxy-carbonyl group which is terminally substituted in the alkyl moiety by a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group or, if R_4 does not denote an aminosulphonyl-phenyl or N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl-phenyl group, it may also denote a di-(C_{1-2}-alkyl)-aminocarbonyl group,

R_3 denotes a C_{1-4}-alkyl group or a phenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl, hydroxy or C_{1-3}-alkoxy group,

R_4 denotes a C_{5-6}cycloalkyl group,

wherein the methylene group in position 4 of the cyclohexyl group may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group,

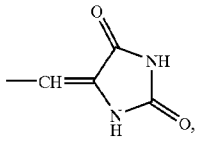
a phenyl group, a phenyl group disubstituted by C_{1-3}-alkyl, C_{1-3}-alkoxy or nitro groups, wherein the substituents may be identical or different, or

a phenyl group substituted by the group R_6, which may additionally be substituted by a fluorine, chlorine or bromine atom or by an amino or nitro group, wherein R_6 denotes a fluorine, chlorine or bromine atom,

a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro, amino or C_{5-6}-cycloalkyl group,

a pyrrolyl, pyrazolyl, imidazolyl, triazolyl or tetrazolyl group bound via a carbon atom, wherein the abovementioned heteroaromatic groups in the carbon skeleton may be substituted by a C_{1-3}-alkyl group or a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group,

the group of formula



a carboxy, C_{1-4}-alkoxycarbonyl, phenyl-C_{1-3}-alkylamino-carbonyl or C_{5-7}-cycloalkyl-carbonyl group,

a 5 or 6-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an —NH or —N(C_{1-3}-alkyl) group,

an unbranched C_{1-3}-alkyl group terminally substituted by the group R_7, wherein

R_7 denotes a C_{5-7}-cycloalkyl group,

wherein in a 5 or 6-membered cycloalkyl group a —$(CH_2)_2$ group may be replaced by a —CO—NH group, a $CH_2)_3$ group may be replaced by an —NH—CO—NH— or a —$(CH_2)_4$ group may be replaced by an —NH—CO—NH—CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl group,

a phenyl or pyridinyl group or a pyrrolyl, pyrazolyl, imidazolyl or triazolyl group bound via a carbon or nitrogen atom, wherein the abovementioned heteroaromatic groups in the carbon skeleton may be substituted by a C_{1-3}-alkyl group or a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl group,

a hydroxy or C_{1-3}-alkoxy group,

an amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)-amino, phenylamino, N-phenyl-C_{1-3}-alkylamino, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group,

a ω-hydroxy-C_{2-3}-alkyl-amino, N—(C_{1-3}-alkyl)-ω-hydroxy-C_{2-3}-alkylamino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino or di-(ω-(C_{1-3}-alkoxy)-C_{2-3}-alkyl)-amino group,

a C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a C_{1-3}-alkylsulphonylamino, N—(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino, C_{1-3}-alkylsulphonylamino-C_{2-3}-alkylamino or C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a hydroxycarbonyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-hydroxycarbonyl-C_{1-3}-alkyl-amino group,

a guanidino group wherein a hydrogen atom may be replaced by a C_{1-3}-alkyl group,

a group of formula

$$—N(R_8)—CO—(CH_2)_n—R_9 \quad (II),$$

wherein

R_8 denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R_9 denotes an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino or C_{1-4}-alkoxy group, a 5- or 6-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an —NH, —N(C_{1-3}-alkyl) or —N(C_{1-3}-alkyl-carbonyl) group, or, if n denotes one of the numbers 1, 2 or 3, R_9 may also denote a hydrogen atom,

a group of formula

$$—N(R_{10})—(CH_2)_m—(CO)_o—R_{11} \quad (III),$$

wherein

R_{10} denotes a hydrogen atom or a C_{1-3}-alkyl group,

m denotes one of the numbers 1, 2 or 3,

o denotes the number 1 or, if m is one of the numbers 2 or 3, o may also denote the number 0 and

R_{11} denotes an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-4}-alkoxy or methoxy-C_{1-3}-alkoxy group or a 5- or 6-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an —NH, —N(C_{1-3}-alkyl) or —N(C_{1-3}-alkyl-carbonyl) group,

an azetidino, pyrrolidino, piperidino, 2,6-dimethyl-piperidino, 3,5-dimethyl-piperidino or azepino group, wherein

the methylene group in position 3 of the pyrrolidino group may be substituted by a hydroxy group,

the methylene group in position 4 of the piperidino group may be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl or C_{1-3}-alkoxy group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(C_{1-3}-alkyl-carbonyl), —N(benzoyl) or —N(phenyl-C_{1-3}-alkyl-carbonyl) group,

wherein a methylene group linked to an imino-nitrogen atom of the pyrrolidino, piperidino or piperazino group may be replaced by a carbonyl group,

or R_6 denotes a straight-chain C_{1-3}-alkyl group which is terminally substituted by a carboxy or C_{1-3}-alkoxy-carbonyl group,

a group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein

R_{12} denotes a hydrogen atom, a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group,

p denotes one of the numbers 0, 1 or 2 and

R_{13} denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, benzylamino, N—(C_{1-3}-alkyl)-benzylamino, C_{1-3}-alkoxy-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-C_{1-3}-alkoxy-C_{1-3}-alkylamino, di-(2-methoxy-ethyl)-amino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino or aminocarbonyl-methyl-N-(methyl)-amino group,

a pyrrolyl, pyrazolyl or imidazolyl group bound via a nitrogen atom and optionally substituted by a C_{1-3}-alkyl group,

a pyrrolidino, piperidino, morpholino, thiomorpholino or a piperazino group optionally substituted in the 4 position by a C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl or C_{1-4}-alkoxycarbonyl group or, if n denotes the number 1 or 2, it may also denote a hydrogen atom,

a group of formula

$$—N(R_{14})—(CH_2)_q—(CO)_r—R_{15} \quad (V),$$

wherein

R_{14} denotes a hydrogen atom, a C_{1-4}-alkyl, C_{1-3}-alkyl-carbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, furyl-carbonyl, pyridinyl-carbonyl, furyl-C_{1-3}-alkyl-carbonyl, pyridinyl-C_{1-3}-alkylcarbonyl, C_{1-4}-alkylsulphonyl, phenylsulphonyl or phenyl-C_{1-3}-alkylsulphonyl group,

q denotes one of the numbers 1, 2 or 3,

r denotes the number 1 or, if q is one of the numbers 2 or 3, it may also denote the number 0 and

R_{15} denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino, N—(C_{1-4}-alkyl)-phenylamino, benzylamino or N—(C_{1-4}-alkyl)-benzylamino group,

or a group of formula

$$—N(R_{16})—SO_2—R_{17} \quad (VI),$$

wherein

R_{16} denotes a hydrogen atom or a C_{1-3}-alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or N—(C_{1-3}-alkyl)-trifluoromethyl-carbonyl-amino group and

R_{17} denotes a C_{1-3}-alkyl group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R_6 may be substituted by a fluorine, chlorine or bromine atom, by a methyl, trifluoromethyl, methoxy, nitro or cyano group and

R_5 denotes a hydrogen atom,

wherein a hydrogen atom bound to a nitrogen atom in the abovementioned groups may be replaced by an acetyl or tert.butoxycarbonyl group,

the carboxy groups contained in the abovementioned groups may also be present in the form of the tert.butoxycarbonyl precursor group and

the saturated alkyl and alkoxy moieties contained in the abovementioned groups, which contain more than 2 carbon atoms, may be straight-chain or branched, unless otherwise stated,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

One subgroup of particularly preferred compounds of general formula I deserving special mention comprises those wherein

X, R_1, R_3 and R_5 are as hereinbefore defined,

R_2 denotes a straight-chain or branched C_{1-4}-alkoxycarbonyl group or a phenoxycarbonyl group,

a straight-chain or branched C_{1-3}-alkoxycarbonyl group, which is terminally substituted in the alkyl moiety by a phenyl-carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group, or

a straight-chain or branched C_{2-3}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkylamino group, and

R_4 denotes an R_7—(n-C_{1-3}-alkyl)-phenyl group, wherein

R_7 denotes an amino, C_{1-6}-alkylamino, di-(C_{1-4}-alkyl)-amino, ω-hydroxy-C_{2-3}-alkyl-amino, N—(C_{1-3}-alkyl)ω-hydroxy-C_{2-3}-alkyl-amino, di-(ω-hydroxy-

C_{2-3}-alkyl)-amino or di-(ω-(C_{1-3}-alkoxy)-C_{2-3}-alkyl)-amino group,

or a phenyl group substituted by the group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein R_{12}, p and R_{13} are as hereinbefore defined,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

A second subgroup of particularly preferred compounds of general formula I deserving special mention comprises those wherein

X, R_1, R_3 and R_5 are as hereinbefore defined,

R_2 denotes an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group or, if R_4 does not denote an aminosulphonyl-phenyl or N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl-phenyl group, R_2 may also denote a di-(C_{1-2}-alkyl)-aminocarbonyl group and

R_4 denotes a R_7—(n-C_{1-3}-alkyl)-phenyl group, wherein

R_7 denotes an amino, C_{1-6}-alkylamino, di-(C_{1-4}-alkyl)-amino, ω-hydroxy-C_{2-3}-alkyl-amino, N—(C_{1-3}-alkyl)-ω-hydroxy-C_{2-3}-alkyl-amino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino or di-(ω-(C_{1-3}-alkoxy)-C_{2-3}-alkyl)amino group,

or a phenyl group substituted by the group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein R_{12}, p and R_{13} are as hereinbefore defined,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

Most particularly preferred compounds of general formula I are those wherein

X denotes an oxygen atom,

R_1 and R_5 each denote a hydrogen atom,

R_2 denotes a methoxycarbonyl, ethoxycarbonyl or aminocarbonyl group,

R_3 denotes a phenyl group and

R_4 denotes a phenyl group monosubstituted by the group R_6, wherein

R_6 denotes an N-methyl-imidazol-2-yl group,

an unbranched C_{1-3}-alkyl group which is terminally substituted by a C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, piperidino or 2,6-dimethyl-piperidino group,

a group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein

R_{12} denotes a C_{1-3}-alkyl group,

p denotes one of the numbers 1 or 2 and

R_{13} denotes a di-(C_{1-3}-alkyl)-amino group,

or a group of formula

$$—N(R_{14})—(CH_2)_q—(CO)_r—R_{15} \quad (V),$$

wherein

R_{14} denotes a C_{1-3}-alkyl-carbonyl or C_{1-3}-alkylsulphonyl group,

q denotes one of the numbers 1, 2 or 3,

r denotes the number 1 or, if q is one of the numbers 2 or 3, r may also denote the number 0 and

R_{15} denotes a di-(C_{1-3}-alkyl)-amino group,

wherein the saturated alkyl moieties contained in the abovementioned groups which contain more than 2 carbon atoms may be straight-chain or branched, unless otherwise stated,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

A subgroup of most particularly preferred compounds of general formula I deserving special mention comprises those wherein

X, R_1, R_3 and R_5 are as hereinbefore defined,

R_2 denotes a methoxycarbonyl or ethoxycarbonyl group and

R_4 denotes a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkylphenyl group or

a phenyl group substituted by the group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein R_{12}, p and R_{13} areas hereinbefore defined,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

The following are mentioned as examples of particularly preferred compounds:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(b) 3-Z-[(1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone,

(c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(d) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(e) 3-Z-[1-(4-((2,6dimethyl-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(f) 3-Z-[1-(4N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(g) 3-Z-[1-(4-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(h) 3-Z-[1-(4(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(i) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(j) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(k) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(l) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(m) 3-Z-[1-(4N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(n) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(o) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(p) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(q) 3-Z-[1-(4(N-((2-dimethylamino-ethyl)carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(r) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and

(s) 3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

the tautomers, the mixtures and the salts thereof.

Another subgroup of compounds of general formula I comprises those wherein X denotes an oxygen or sulphur atom,

R_1 denotes a hydrogen atom or a prodrug group such as a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a carboxy group, a straight-chain or branched C_{1-6}-alkoxycarbonyl group, a C_{5-7}Cycloalkoxycarbonyl or phenyl-C_{1-3}-alkoxycarbonyl group, an aminocarbonyl or C_{1-2}-alkylaminocarbonyl group or, if R_4 does not denote an aminosulphonyl-phenyl or N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl-phenyl group, a di-(C_{1-2}-alkyl)-aminocarbonyl group,

R_3 denotes a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl or heteroaryl group,

a phenyl or naphthyl group, a phenyl or naphthyl group mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group, whilst in the event of disubstitution the substituents may be identical or different and wherein the abovementioned unsubstituted as well as the mono- and disubstituted phenyl and naphthyl groups may additionally be substituted

by a hydroxy, hydroxy-C_{1-3}-alkyl or C_{1-3}-alkoxy-C_{1-3}-alkyl group,

by a cyano, carboxy, carboxy-C_{1-3}-alkyl, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

by a nitro group,

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino or amino-C_{1-3}-alkyl group,

by a C_{1-3}-alkylcarbonylaamino, N—(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl, N—(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl, C_{1-3}-alkyl-sulphonylamino, C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl, N—(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl or aryl-C_{1-3}-alkylsulphonylamino group,

by a cycloalkylamino, cycloalkyleneimino, cycloalkyleneiminocarbonyl, cycloalkyleneimino-C_{1-3}-alkyl, cycloalkyleneiminocarbonyl-C_{1-3}-alkyl or cycloalkyleneiminosulphonyl-C_{1-3}-alkyl group having 4 to 7 ring members in each case, whilst in each case the methylene group in position 4 of a 6 or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH or —N(C_{1-3}-alkyl) group,

or by a heteroaryl or heteroaryl-C_{1-3}-alkyl group,

R_4 denotes a C_{3-7}-cycloalkyl group,

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group,

or a phenyl group substituted by the group R_6, which may additionally be substituted by a fluorine, chlorine, bromine or iodine atom, by a C_{1-5}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminosulphonyl, nitro or cyano group, wherein

R_6 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

a cyano, nitro, C_{1-5}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or heteroaryl group,

a C_{1-3}-alkoxy group optionally substituted by 1 to 3 fluorine atoms, a C_{1-3}-alkoxy-C_{1-3}-alkoxy, phenyl-C_{1-3}-alkoxy, amino-C_{2-3}-alkoxy, C_{1-3}-alkylamino-C_{2-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{2-3}-alkoxy, phenyl-C_{1-3}-alkylamino-C_{2-3}-alkoxy, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino-C_{2-3}-alkoxy, C_{5-7}-cycloalkyleneimino-C_{2-3}-alkoxy or C_{1-3}-alkylmercapto group,

a carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl, phenyl-C_{1-3}-alkylamino-carbonyl, N—(C_{1-3}-alkyl)phenyl-C_{1-3}-alkylamino-carbonyl, piperazinocarbonyl or N—(C_{1-3}-alkyl)-piperazinocarbonyl group,

a C_{1-3}-alkylaminocarbonyl or N—(C_{1-5}-alkyl)-C_{1-3}-alkylaminocarbonyl group wherein an alkyl moiety is substituted by a carboxy or C_{1-3}-alkoxycarbonyl group or is substituted in the 2 or 3 position by a di-(C_{1-3}-alkyl)-amino, piperazino, N—(C_{1-3}-alkyl)-piperazino or a 4- to 7-membered cycloalkyleneimino group,

a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused to a phenyl ring or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in the 4 position of a 6 or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group,

a C_{1-4}-alkyl group which may be substituted

by a hydroxy or C_{1-3}-alkoxy group,

by an amino, C_{1-7}-alkylamino, di-(C_{1-7}-alkyl)-amino, di-N—(C_{1-3}-alkyl)-amino-C_{2-3}-alkylamino, tri-N,N,N'-C_{1-3}-alkyl)-amino-C_{2-3}-alkylamino, phenylamino, N-phenyl-C_{1-3}-alkyl-amino, phenyl-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

by a C_{1-3}-alkylcarbonylamino, N—(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl) C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group,

by a C_{4-7}-cycloalkylamino, C_{4-7}-cycloalkyl-C_{1-3}-alkylamino or C_{4-7}-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond and wherein the abovementioned groups may each additionally be substituted at the amino-nitrogen atom by a C_{1-3}-alkyl group wherein some or all of the hydrogen atoms are replaced by fluorine atoms, by a C_{5-7}-cycloalkyl, C_{2-4}-alkenyl or C_{1-4}-alkyl group,

by a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo,

pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a nitro, C_{1-3}-alkyl, C_{1-3}-alkoxy or amino group or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group,

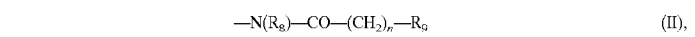
by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or

by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

an amino, pyrrolidino, piperidino, morpholino, benzoylamino or N—(C_{1-3}-alkyl)-benzoylamino group,

an N—(C_{1-3}-alkyl)-C_{2-4}-alkanoylamino group which is additionally substituted in the alkyl moiety by a carboxy or C_{1-3}-alkoxycarbonyl group,

a group of formula



$$—N(R_8)—CO—(CH_2)_n—R_9 \quad (II),$$

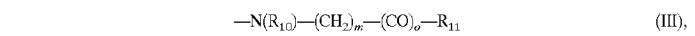
wherein

R_8 denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R_9 denotes an amino, C_{1-4}-alkylamino, phenylamino, N—(C_{1-4}-alkyl)-phenylamino, benzylamino, N—(C_{1-4}-alkyl)-benzylamino or di-(C_{1-4}-alkyl)-amino group, a 4- to 7-membered cycloalkyleneimino group, whilst in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkylcarbonyl) or —N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula



$$—N(R_{10})—(CH_2)_m—(CO)_o—R_{11} \quad (III),$$

wherein

R_{10} denotes a hydrogen atom, a C_{1-3}-alkyl group, a C_{1-3}-alkylcarbonyl, arylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, C_{1-3}-alkylsulphonyl, arylsulphonyl or phenyl-C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2, 3 or 4,

o denotes one of the numbers 0 or 1 and

R_{11} denotes an amino, C_{1-4}-alkylamino, phenylamino, N—(C_{1-4}-alkyl)-phenylamino, benzylamino, N—(C_{1-4}-alkyl)-benzylamino or di-(C_{1-4}-alkyl)-amino group, a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group, a C_{1-3}-alkoxy group or a di-(C_{1-4}alkyl)-amino-C_{1-3}-alkylamino group optionally substituted in the 1 position by a C_{1-3}-alkyl group,

or an N—(C_{1-3}-alkyl)-C_{1-5}-alkylsulphonylamino or N—(C_{1-3}-alkyl)-phenylsulphonylamino group wherein the alkyl moiety is additionally substituted by a cyano or carboxy group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R_6 may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-5}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group,

and

R_5 denotes a hydrogen atom or a C_{1-3}-alkyl group,

wherein by an aryl group is meant a phenyl or naphthyl group optionally mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group and

by a heteroaryl group is meant a monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C_{1-3}-alkyl group, wherein the 6-membered heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C_{1-3}-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms, and moreover a phenyl ring may be fused to the abovementioned monocyclic heterocyclic groups via two adjacent carbon atoms,

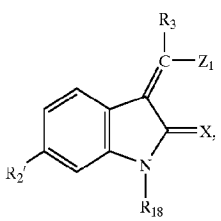
the saturated alkyl and alkoxy moieties present in the groups defined above which contain more than 2 carbon atoms also include the branched isomers thereof such as, for example, the isopropyl, tert.butyl or isobutyl group, unless otherwise stated, and

additionally any carboxy, amino or imino group present may be substituted by a group which can be cleaved in vivo,

the isomers and the salts thereof.

According to the invention the new compounds are obtained, for example, by the following methods known in principle from the literature:

a. reacting a compound of general formula



(VII)

wherein

X and R_3 are as hereinbefore defined,

R_2' has the meanings given for R_2 hereinbefore,

R_{18} denotes a hydrogen atom or a protecting group for the nitrogen atom of the lactam group, wherein one

of the groups R_2' and R_{18} may also denote a bond to a solid phase optionally formed via a spacer and the other one of the groups R_2' and R_{18} has the above-mentioned meanings, and Z_1 denotes a halogen atom, a hydroxy, alkoxy or aryl-alkoxy group, e.g. a chlorine or bromine atom, a methoxy, ethoxy or benzyloxy group,

with an amine of general formula

(VIII)

wherein

R_4 and R_5 are as hereinbefore defined, and if necessary subsequently cleaving any protecting group used for the nitrogen atom of the lactam group or cleaving from a solid phase.

The protecting group for the nitrogen atom of the lactam group may be, for example, an acetyl, benzoyl, ethoxycarbonyl, tert.butyloxycarbonyl or benzyloxycarbonyl group and the solid phase may be a resin such as a 4-(2',4'-dimethoxyphenylaminomethyl)-phenoxy resin, the bond preferably being formed via the amino group, or a p-benzyloxybenzyl alcohol resin, wherein the bond is conveniently formed via an intermediate member such as a 2,5-dimethoxy-4-hydroxy-benzyl derivative.

The reaction is conveniently carried out in a solvent such as dimethylformamide, toluene, acetonitrile, tetrahydrofuran, dimethylsulphoxide, methylene chloride or mixtures thereof, optionally in the presence of an inert base such as triethylamine, N-ethyl-diisopropylamine or sodium hydrogen carbonate at temperatures between 20 and 175° C., whilst any protecting group used can be cleaved at the same time by transamidation.

If Z_1 in a compound of general formula VII denotes a halogen atom, the reaction is preferably carried out in the presence of an inert base at temperatures of between 20 and 120° C.

If Z_1 in a compound of general formula VII denotes a hydroxy, alkoxy or arylalkoxy group, the reaction is preferably carried out at temperatures between 20 and 200° C.

If a protecting group used subsequently has to be cleaved, this is conveniently done either hydrolytically in an aqueous or alcoholic solvent, e.g. in methanol/water, ethanol/water, isopropanol/water, tetrahydrofuran/water, dioxan/water, dimethylformamide/water, methanol or ethanol in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide at temperatures between 0 and 100° C., preferably at temperatures between 10 and 50° C.,

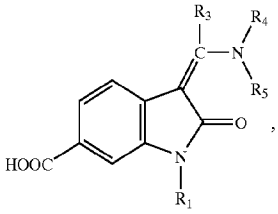
or advantageously by transamidation with an organic base such as ammonia, butylamine, dimethylamine or piperidine in a solvent such as methanol, ethanol, dimethylformamide and the mixtures thereof or in an excess of the amine used, at temperatures between 0 and 100° C., preferably at temperatures between 10 and 50° C.

Cleaving from any solid phase used is preferably carried out using trifluoroacetic acid and water at temperatures between 0 and 35° C., preferably at ambient temperature.

b. In order to prepare a compound of general formula I wherein R_2 has the meanings given hereinbefore, with the exception of the carboxy group:

reacting a compound of general formula

(IX)



wherein

R_1 and R_3 to R_5 are as hereinbefore defined, or the reactive derivatives thereof, with a compound of general formula

$$H—R_{19} \quad (X),$$

wherein

R_{19} denotes a C_{1-6}-alkanol, a C_{4-7}-cycloalkanol or an aromatic alcohol,

a C_{1-6}-alkanol which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C_{1-3}-alkoxy-carbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a C_{2-6}-alkanol which is terminally substituted in the alkyl moiety by a chlorine atom or a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an amino or methylamino group, an ethylamino group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group or a di-(C_{1-2}-alkyl)amino group.

The esterification or amidation is preferably carried out in a solvent such as methylene chloride, diethylether, tetrahydrofuran, toluene, dioxan, acetonitrile, dimethylsulphoxide or dimethylformamide, optionally in the presence of an inorganic or a tertiary organic base, preferably at temperatures between 20° C. and the boiling temperature of the solvent used. The reaction with a corresponding acid is preferably carried out in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionylchloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexyl-carbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexyl-carbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine, conveniently at temperatures between 0 and 150° C., preferably at temperatures between 0 and 100° C., and the acylation with a corresponding reactive compound such as an anhydride, ester, imidazolide or halide thereof, is optionally carried out in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures between 0 and 150° C., preferably at temperatures between 50 and 100° C.

c. In order to prepare a compound of general formula I, wherein R_4 denotes a C_{1-4}-alkyl group substituted by the group R_7, wherein

R_7 denotes an amino, C_{1-7}-alkylamino, di-(C_{1-7}-alkyl)-amino, phenylamino, N-phenyl-C_{1-3}-alkyl-amino, phenyl-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

a ω-hydroxy-C_{2-3}-alkyl-amino, N—(C_{1-3}-alkyl)-ω-hydroxy-C_{2-3}-alkyl-amino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino, di-(ω-(C_{1-3}-alkoxy)-C_{2-3}-alkyl)-amino or N-(dioxolan-2-yl)-C_{1-3}-alkyl-amino group,

a C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a C_{1-3}-alkylsulphonylamino, N—(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino, C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a group of formula

$$—N(R_{10})—(CH_2)_m—(CO)_o—R_{11} \quad (III),$$

wherein

R_{10} denotes a hydrogen atom, a C_{1-3}-alkyl group, a C_{1-3}-alkylcarbonyl, arylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, C_{1-3}-alkylsulphonyl, arylsulphonyl or phenyl-C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2, 3 or 4,

o denotes the number 1 and

R_{11} denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino, N—(C_{1-4}-alkyl)-phenylamino, benzylamino, N—(C_{1-4}-alkyl)-benzylamino,

C_{1-4}-alkoxy or C_{1-3}-alkoxy-C_{1-3}-alkoxy group, a di-(C_{1-4}-alkyl)-amino-C_{1-3}-alkylamino group optionally substituted in the 1 position by a C_{1-3}-alkyl group, or a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group,

a C_{4-7}-cycloalkylamino, C_{4-7}-cycloalkyl-C_{1-3}-alkylamino or C_{4-7}-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond and wherein the abovementioned groups may each additionally be substituted at the amino-nitrogen atom by a C_{5-7}-cycloalkyl, C_{2-4}-alkenyl or C_{1-4}-alkyl group,

or a 4- to 7-membered cycloalkyleneimino group, wherein

the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a nitro, C_{1-3}-alkyl, C_{1-3}-alkoxy or amino group, and/or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and/or

the methylene group in the 3 position of a 5-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy or C_{1-3}-alkoxy-C_{1-3}-alkyl group,

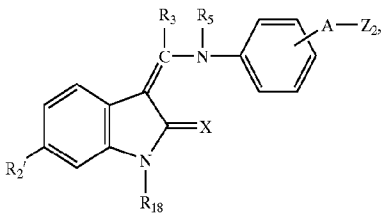
in each case the methylene group in the 3 or 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkoxy-C_{1-3}-alkyl, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl-), —N(phenyl), —N(phenyl-C_{1-3}-alkyl-), —N(C_{1-3}-alkyl-carbonyl-), —N(C_{1-4}-alkoxy-carbonyl-), —N(benzoyl-) or —N(phenyl-C_{1-3}-alkyl-carbonyl-) group,

wherein a methylene group linked to an imino-nitrogen atom of the cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl group or in a 5- to 7-membered monocyclic cycloalkyleneimino group or a cycloalkyleneimino group fused to a phenyl group the two methylene groups linked to the imino-nitrogen atom may each be replaced by a carbonyl group:

reacting a compound of general formula

(XI)



wherein

R_3, R_5 and X are as hereinbefore defined,

R_2' has the meanings given for R_2 hereinbefore,

R_{18} denotes a hydrogen atom or a protecting group for the nitrogen atom of the lactam group, wherein one of the groups R_2' and R_{18} may also denote a bond to a solid phase optionally formed via a spacer and the other one of the groups R_2' and R_{18} has the abovementioned meanings, A denotes a C_{1-4}-alkyl group and Z_2 denotes a leaving group, for example an alkyl or arylsulphonyloxy group such as the methylsulphonyloxy, ethylsulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy group, with an amine of general formula

$$H—R_7, \quad (XII),$$

wherein

R_7, has the meanings given for R_7 hereinbefore, and subsequently, if necessary, cleaving any protecting group used for the nitrogen atom of the lactam group, or cleaving from a solid phase.

The reaction is conveniently carried out in a solvent such as methylene chloride, tetrahydrofuran, 1,4-dioxan, toluene, acetonitrile, dimethylsulphoxide, dimethylformamide, dimethylacetamide, N-methylpyrrolidone or the mixtures thereof, optionally with the saddition of water as a co-solvent and/or with the addition of an inert auxiliary base, e.g. sodium hydrogen carbonate, pyridine, 2,4,6-trimethylpyridine, quinoline, triethylamine, N-ethyldiisopropylamine, N-ethyl-dicyclohexylamine, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo[5,4,0]undec-7-ene, at temperatures between −50° C. and +100° C., preferably between −10° C. and +50° C., while any protecting group used may be cleaved at the same time by transamidation.

If any protecting group used for the nitrogen atom of the lactam group has to be removed or if the compound has to

be cleaved from a solid phase this is carried out as described under method (a) above.

If according to the invention a compound of general formula I is obtained which contains an alkoxycarbonyl group, this may be converted by hydrolysis into a corresponding carboxy compound, or

if a compound of general formula I is obtained which contains an amino or alkylamino group, this may be converted by reductive alkylation into a corresponding alkylamino or dialkylamino compound, or

if a compound of general formula I is obtained which contains an amino or alkylamino group, this may be converted by acylation or sulphonation into a corresponding acyl or sulphonyl compound, or

if a compound of general formula I is obtained which contains a carboxy group, this may be converted by esterification or amidation into a corresponding ester or aminocarbonyl compound, or

if a compound of general formula I is obtained which contains a cycloalkyleneimino group wherein a methylene group is replaced by a sulphur atom, this may be converted by oxidation into a corresponding sulphinyl or sulphonyl compound, or

if a compound of general formula I is obtained which contains a nitro group, this may be converted by reduction into a corresponding amino compound, or

if a compound of general formula I is obtained wherein R_4 denotes a phenyl group substituted by an amino, alkylamino, aminoalkyl or N-alkyl-amino group, this may subsequently be converted, by reaction with a corresponding cyanate, isocyanate or carbamoyl halide, into a corresponding urea compound of general formula I, or

if a compound of general formula I is obtained wherein R_4 denotes a phenyl group substituted by an amino, alkylamino, aminoalkyl or N-alkyl-amino group, this may subsequently be converted, by reaction with a corresponding compound which transfers the amidino group or by reaction with a corresponding nitrile, into a corresponding guanidino compound of general formula I.

The subsequent hydrolysis is preferably carried out in an aqueous solvent, e.g. in water, methanol/water, ethanol/water, isopropanol/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide at temperatures between 0 and 100° C., preferably at temperatures between 10 and 50° C.

The subsequent reductive alkylation is preferably carried out in a suitable solvent such as methanol, methanol/water, methanol/water/ammonia, ethanol, ether, tetrahydrofuran, dioxan or dimethylformamide, optionally with the addition of an acid such as hydrochloric acid in the presence of catalytically activated hydrogen, e.g. hydrogen in the presence of Raney nickel, platinum or palladium/charcoal, or in the presence of a metal hydride such as sodium borohydride, lithium borohydride, sodium cyanoborohydride or lithium aluminium hydride at temperatures between 0 and 100° C., preferably at temperatures between 20 and 80° C.

The subsequent acylation or sulphonylation is preferably carried out with the corresponding free acid or a corresponding reactive compound such as the anhydride, ester, imidazolide or halide thereof, preferably in a solvent such as methylene chloride, diethylether, tetrahydrofuran, toluene, dioxan, acetonitrile, dimethylsulphoxide or dimethylformamide, optionally in the presence of an inorganic or tertiary organic base at temperatures between −20 and 200° C., preferably at temperatures between 20° C. and boiling temperature of the solvent used. The reaction with the free acid may optionally be carried out in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylamino-pyridine, N-methyl-morpholine or triethylamine, conveniently at temperatures between 0 and 150° C., preferably at temperatures between 0 and 100° C. The reaction with a corresponding reactive compound may optionally be carried out in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine, N-methyl-morpholine or pyridine or by using an anhydride in the presence of the corresponding acid at temperatures between 0 and 150° C., preferably at temperatures between 50 and 100° C.

The subsequent esterification or amidation is conveniently carried out by reacting a corresponding reactive carboxylic acid derivative with a corresponding alcohol or amine as described hereinbefore.

The subsequent oxidation of the sulphur atom is preferably carried out in a solvent or mixture of solvents, e.g. in water, water/pyridine, acetone, methylene chloride, acetic acid, acetic acid/acetic anhydride, dilute sulphuric acid or trifluoroacetic acid, usefully at temperatures of between −80 and 100° C. depending on the oxidising agent used.

In order to prepare a corresponding sulphinyl compound of general formula I the oxidation is expediently carried out with one equivalent of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid, trifluoroacetic acid or formic acid at 0 to 20° C. or in acetone at 0 to 60° C., with a peracid such as performic acid in glacial acetic acid or trifluoroacetic acid at 0 to 50° C. or with m-chloroperbenzoic acid in methylene chloride, chloroform or dioxan at −20 to 80° C., with sodium metaperiodate in aqueous methanol or ethanol at −15 to 25° C., with bromine in glacial acetic acid or aqueous acetic acid optionally in the presence of a weak base such as sodium acetate, with N-bromosuccinimide in ethanol, with tert.butyl hypochlorite in methanol at −80 to −30° C., with iodobenzodichloride in aqueous pyridine at 0 to 50° C., with nitric acid in glacial acetic acid at 0 to 20° C., with chromic acid in glacial acetic acid or in acetone at 0 to 20° C. and with sulphuryl chloride in methylene chloride at −70° C., the resulting thioether-chlorine complex is expediently hydrolysed with aqueous ethanol.

In order to prepare a sulphonyl compound of general formula I the oxidation is expediently carried out starting from a corresponding sulphinyl compound with one or more equivalents of the oxidising agent used or starting from a corresponding mercapto compound, expediently with two or more equivalents of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid/acetic anhydride, trifluoroacetic acid or in formic acid at 20 to 100° C. or in acetone at 0 to 60° C., with a peracid such as performic acid

or m-chloroperbenzoic acid in glacial acetic acid, trifluoroacetic acid, methylene chloride or chloroform at temperatures between 0 and 60° C., with nitric acid in glacial acetic acid at 0 to 20° C., with chromic acid, sodium periodate or potassium permanganate in acetic acid, water/sulphuric acid or in acetone at 0 to 20° C.

The subsequent reduction of a nitro group is preferably carried out by hydrogenolysis, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal or Raney nickel in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid or glacial acetic acid at temperatures of between 0 and 50° C., but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar.

The subsequent preparation of a corresponding urea compound of general formula I is conveniently carried out with an inorganic cyanate or a corresponding isocyanate or carbamoylchloride, preferably in a solvent such as dimethylformamide and optionally in the presence of a tertiary organic base such as triethylamine at temperatures between 0 and 50° C., preferably at ambient.

The subsequent preparation of a corresponding guanidino compound of general formula I is conveniently carried out by reacting with a compound which transfers the amidino group such as 3,5-dimethylpyrazole-1-carboxylic acid amidine, preferably in a solvent such as dimethylformamide and optionally in the presence of a tertiary organic base such as triethylamine at temperatures of between 0 and 50° C., preferably at ambient temperature.

In the reactions described hereinbefore, any reactive groups present such as carboxy, hydroxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

protecting groups for a hydroxy, amino, alkylamino or imino group may be an acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxan/water, in the presence of a acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide, at temperatures between 0 and 100° C., preferably at temperatures between 10 and 50° C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid or glacial acetic acid at temperatures between 0 and 50° C., but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar.

A methoxybenzyl group may also be cleaved in the presence of an oxidising agent such as cerium(IV) anmmonium nitrate in a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures of between 0 and 50° C., but preferably at ambient temperature.

A 2,4dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxan, ethyl acetate or ether.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxan at temperatures between 20 and 50° C.

Moreover, chiral compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers.

Thus, for example, the compounds of general formula I obtained which occur as racemates may be separated by methods known per se (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the mixture of diastereomeric salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, N-acetylglutarnic acid, aspartic acid, N-acetylaspartic acid or quinic acid. An optically active alcohol may be for example (+)- or (−)-menthol and an optically active acyl group in arnides, for example, may be a (+)- or (−)-menthyloxycarbonyl group.

Furthermore, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, maleic acid or methanesulphonic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae VII to XII used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature or may be obtained by the methods described hereinbefore and in the Examples. For example, the com-

pounds of general formula VI are described in German Patent Application 198 24 922.5.

Moreover, the compounds of general formula XI may be obtained from the compounds of general formula I wherein R_4 denotes a C_{1-4}-alkyl-phenyl group substituted in the alkyl moiety by a hydroxy group, for example, by reacting with alkyl- or arylsulphonyl-chlorides.

As already mentioned, the new compounds of general formula I wherein R_1 denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, particularly inhibitory effects on various kinases, especially on receptor-tyrosine kinases such as VEGFR2, PDGFRα, PDGFRβ, FGFR1, FGFR3, EGFR, HER2, IGF1R and HGFR, as well as on complexes of CDK's (Cyclin Dependent Kinases) such as CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8 and CDK9 with their specific cyclins (A, B1, B2, C, D1, D2, D3, E, F, G1, G2, H, I and K) and on viral cyclin, on the proliferation of cultivated human cells, particularly endothelial cells, e.g. in angiogenesis, but also on the proliferation of other cells, particularly tumour cells.

The biological properties of the new compounds were tested by the following standard procedure, as follows:

Human umbilical endothelial cells (HUVEC) were cultivated in IMDM (Gibco BRL), supplemented with 10% foetal calf serum (FBS) (Sigma), 50 μM of β-mercaptoethanol (Fluka), standard antibiotics, 15 μg/ml of endothelial cell growth factor (ECGS, Collaborative Biomedical Products) and 100 μg/ml of heparin (Sigma) on gelatine-coated culture dishes (0.2% gelatine, Sigma) at 37° C., under 5% CO_2 in a water-saturated atmosphere.

In order to investigate the inhibitory activity of the compounds according to the invention the cells were starved for 16 hours, i.e. kept in culture medium without growth factors (ECGS+heparin). The cells were detached from the culture dishes using trypsin/EDTA and washed once in serumontaining medium. Then they were seeded out in amounts of 2.5×10^3 cells per well.

The proliferation of the cells was stimulated with 5 ng/ml of $VEGF_{165}$ (vascular endothelial growth factor; H. Weich, GBF Braunschweig) and 10 μg/ml of heparin. As a control, 6 wells in each dish were not stimulated.

The compounds according to the invention were dissolved in 100% dimethylsulphoxide and added to the cultures in various dilutions in triplicate, the maximum dimethyl sulphoxide concentration being 0.3%.

The cells were incubated for 76 hours at 37° C., then for a further 16 hours ^{3}H-thymidine (0.1 μCi/well, Amersham) was added in order to determine the DNA synthesis. Then the radioactively labelled cells were immnobilised on filter mats and the radioactivity incorporated was measured in a β-counter. In order to determine the inhibitory activity of the compounds according to the invention the mean value of the non-stimulated cells was subtracted from the mean value of the factor-stimulated cells (in the presence or absence of the compounds according to the invention).

The relative cell proliferation was calculated as a percentage of the control (HUVEC without inhibitor) and the concentration of active substance which inhibits the proliferation of the cells by 50% (IC_{50}) was determined.

The test results of the following compounds (a) to (s) of general formula I are given by way of example:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(b) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone,

(c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(d) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(e) 3-Z-[1-(4-((2,6-dimethyl-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(f) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(g) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(h) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(i) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(j) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(k) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6methoxycarbonyl-2-indolinone,

(l) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(m) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(n) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(o) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6methoxycarbonyl-2-indolinone,

(p) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(q) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(r) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and

(s) 3-Z-[1-(4methylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone.

The following Table contains the results found:

Compound	IC_{50} [μm]
(a)	0.04
(b)	0.35
(c)	0.01
(d)	0.02
(e)	0.05
(f)	0.01
(g)	0.003
(h)	0.01
(i)	0.03
(j)	0.02
(k)	0.03
(l)	0.1
(m)	0.02
(n)	0.02
(o)	0.01
(p)	0.02
(q)	0.02
(r)	0.01
(s)	0.04

In view of their inhibitory effect on the proliferation of cells, particularly endothelial cells and tumour cells, the

compounds of general formula I are suitable for treating diseases in which the proliferation of cells, particularly endothelial cells, plays a part.

Thus, for example, the proliferation of endothelial cells and the concomitant neovascularisation constitute a crucial stage in tumour progression (Folkman J. et al., Nature 339, 58–61, (1989); Hanahan D. and Folkman J., Cell 86, 353–365, (1996)). Furthermore, the proliferation of endothelial cells is also important in haemangiomas, in metastasisation, rheumatoid arthritis, psoriasis and ocular neovascularisation (Folkman J., Nature Med. 1, 27–31, (1995)). The therapeutic usefulness of inhibitors of endothelial cell proliferation was demonstrated in the animal model for example by O'Reilly et al. and Parangi et al. (O'Reilly M. S. et al., Cell 88, 277–285, (1997); Parangi S. et al., Proc Natl Acad Sci USA 93, 2002–2007, (1996)).

The compounds of general formula I, their tautomers, their stereoisomers or the physiologically acceptable salts thereof are thus suitable, for example, for treating tumours (e.g. plate epithelial carcinoma, astrocytoma, Kaposis sarcoma, glioblastoma, lung cancer, bladder cancer, carcinoma of the neck, melanoma, ovarian cancer, prostate cancer, breast cancer, small-cell lung cancer, glioma, colorectal carcinoma, urogenital cancer and gastrointestinal carcinoma as well as haematological cancers, such as multiple myeloma), psoriasis, arthritis (e.g. rheumatoid arthritis), haemangioma, angiofibroma, eye diseases (e.g. diabetic retinopathy), neovascular glaucoma, kidney diseases (e.g. glomerulonephritis), diabetic nephropathy, malignant nephrosclerosis, thrombic microangiopathic syndrome, transplant rejections and glomerulopathy, fibrotic diseases (e.g. cirrhosis of the liver), mesangial cell proliferative diseases, arteriosclerosis and damage to the nerve tissue and also for inhibiting the reocclusion of blood vessels after treatment with a balloon catheter, in vascular prosthetics or after the insertion of mechanical devices for keeping blood vessels open (e.g. stents), or other diseases in which cell proliferation or angiogenesis are involved.

By reason of their biological properties the compounds according to the invention may be used on their own or in conjunction with other pharmacologically active compounds, for example in tumour therapy, in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g. etoposide), mitosis inhibitors (e.g. vinblastin, taxol), compounds which interact with nucleic acids (e.g. cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g. tamoxifen), inhibitors of metabolic processes (e.g. 5-FU etc.), cytokines (e.g. interferons), kinase inhibitors, antibodies, or in conjunction with radiotherapy, etc. These combinations may be administered either simultaneously or sequentially.

For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01–100 mg/kg of body weight, preferably 0.1–20 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, injectable solutions, ampoules, suspensions, solutions, sprays or suppositories.

The Examples which follow are intended to illustrate the invention:

Abbreviations used:

FMOC=9-fluorenylmethoxycarbonyl

HOBt=1-hydroxy-1H-benzotriazole

TBTU=O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium-tetrafluoroborate

DBU=1,8-diazabicyclo[5.4.0]undec-7-ene

Preparation of the starting compounds:

SOLID PHASE EXAMPLE I

2.0 g of Rink resin (MBHA resin, made by Messrs Novabiochem) are left to swell in 30 ml of dimethylformamide. Then 40 ml of 30% piperidine in dimethylformamide are added and the mixture is shaken for 7 minutes to cleave the FMOC protecting group. The resin is then washed repeatedly with dimethylformamide. Then 0.4 g of 2-indolinone-6-carboxylic acid (prepared analogously to Langenbeck et al., Justus Liebigs Ann. Chem. 499, 201–208 (1932)), 297 mg HOBt, 706 mg TBTU and 0.9 ml of Nethyl-diisopropylamine in 30 ml of dimethylformamide are added and the mixture is shaken for 1 hour. Then the solution is suction filtered and the resin is washed five times with 30 ml of dimethylformamide and three times with 30 ml of methylene chloride. To dry it, nitrogen is blown through the resin.

Yield: 1.9 g of charged resin.

SOLID PHASE EXAMPLE II

1.9 g of the resin obtained in Example I are stirred with 6 ml of acetic anhydride and 6 ml of triethyl orthobenzoate for 3 hours at 110° C. Then the mixture is left to cool and the resin is washed with dimethylformamide and subsequently with methylene chloride.

Yield: 1.9 g of moist resin.

The following charged resins are prepared analogously to Example II:

(1) resin charged with 3-Z-(1-ethoxy-methylene)-6-carbamoyl-2-indolinone

Prepared by reacting the resin obtained according to Example I with triethyl orthoformate

(2) resin charged with 3-Z-(1-methoxy-1-methyl-methylene)-6-carbamoyl-2-indolinone

Prepared by reacting the resin obtained according to Example I with trimethyl orthoacetate

(3) resin charged with 3-Z-(1-methoxy-1-ethyl-methylene)-6-carbamoyl-2-indolinone

Prepared by reacting the resin obtained according to Example I with tfimethyl orthopropionate

(4) resin charged with 3-Z-(1-methoxy-1-propyl-methylene)-6-carbamoyl-2-indolinone

Prepared by reacting the product of Example I and trimethyl orthobutyrate

EXAMPLE III

N-(4-nitrophenyl)-N-methyl-methanesulphonamide

3.0 g of N-methyl-4-nitroaniline are dissolved in 20 ml of pyridine and 2.4 g of methanesulphonic acid chloride added dropwise at room temperature. The mixture is stirred for 12 hours at room temperature. After this time the mixture is poured onto water, the precipitate formed is filtered off and dried at 50° C. in vacuo.

Yield: 4.0 g (87% of theory), R_f value: 0.5 (silica gel, ethyl acetate/toluene=7:3).

Melting point: 107–108° C.

EXAMPLE IV

N-(2-dimethylamino-ethyl)-N-methylsulphonyl-4-nitroaniline

38.9 g of N-methylsulphonyl-4-nitroaniline are dissolved in 2.0 l of acetone, 51.9 g of 1-chloro-2-dimethylamino-ethane, 77.4 g of potassium carbonate and 5.0 g of sodium iodide are added and the mixture is stirred for a total of 4 days at 50° C., while after 12 hours a further 25.9 g of 1-chloro-2dimethylamino-ethane, 49.8 g of potassium carbonate and 5.0 g of sodium iodide in 500 ml of acetone are added and after 36 hours another 26.0 g of 1-chloro-2-dimethylamino-ethane, 50.0 g of potassium carbonate and 5.0 g of sodium iodide in 100 ml of acetone are added. After this time the mixture is filtered and the filtrate evaporated down. The residue is stirred with ether, suction filtered and dried at 40° C.

Yield: 25.3 g (49% of theory), R_f value: 0.5 (silica gel, methylene chloride/methanol/ammonia=9:1:0.1) $C_{11}H_{17}N_3O_4S$.

ESI mass spectrum: m/z=288 $[M+H^+]$.

The following compounds are prepared analogously to Example IV:

(1) 4-[N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino]-nitrobenzene

(2) N-carboxymethyl-N-methylsulphonyl-4-nitroaniline

(3) N-cyanomethyl-N-methylsulphonyl-p-phenylenediamine

(4) 4-[N-(2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino]-nitrobenzene

(5) 4-[N-(3-phthalimido-2-yl-propyl)-N-methylsulphonyl-amino]-nitrobenzene

(6) 4-[N-(3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino]-nitrobenzene

EXAMPLE V

N-(dimethylaminocarbonyl-methyl)-N-methylsulphonyl-4-nitroaniline

7.0 g of N-carboxymethyl-N-methylsulphonyl-4-nitroaniline, 2.5 g of dimethylamine hydrochloride, 8.1 g of TBTU and 3.9 g of HOBT are dissolved in 125 ml of dimethylformamide and at 0° C. 17.6 ml of N-ethyl-diisopropylamine are added. The mixture is stirred for 4 hours at room temperature, diluted with 11 l of water and the precipitate formed is suction filtered. After washing with water, ethanol and ether the residue is dried at 70° C. in vacuo.

Yield: 5.3 g (69% of theory), R_f value: 0.40 (silica gel, methylene chloride/methanol=9:1) $C_{11}H_{15}N_3O_5S$.

ESI mass spectrum: m/z=300 $[M-H^-]$.

The following compounds are prepared analogously to Example V:

(1) 4-[(N-dimethylaminocarbonylmethyl)-amino]-nitrobenzene

prepared from 4-(N-carboxymethyl-amino)-nitrobenzene and dimethylamine hydrochloride

(2) 4-(N-methylaminocarbonylmethyl-N-methylsulphonyl-amino)-nitrobenzene

Prepared from N-carboxymethyl-N-methylsulphonyl-4-nitroaniline and methylamine hydrochloride

(3) 4-[(N-(methylcarbamoyl-methyl)-N-methyl-amino)-methyl]-nitrobenzene

Prepared from 4-[(N-carboxymethyl-N-methyl-amino)-methyl]-nitrobenzene and methylamine hydrochloride

(4) 4-[(N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl]-nitrobenzene

Prepared from 4-[(N-carboxymethyl-N-methyl-amino)-methyl]-nitrobenzene and dimethylamine hydrochloride

EXAMPLE VI

4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-nitrobenzene

3.6 g of 4-(2-dimethylamino-ethylamino)-nitrobenzene (according to Gabbay et al., J. Am. Chem. Soc. 91, 5136 (1969)) are dissolved in 50 ml of methylene chloride and 5.0 ml of triethylamine are added. 1.3 ml of acetyl chloride are slowly added dropwise to this mixture at room temperature and the mixture is stirred for 2 hours at room temperature. After this time another 5.0 ml of triethylamine and 1.3 ml of acetylchloride are added and the mixture is refluxed for another 2 hours. The solvent is removed, the residue is taken up in ethyl acetate and the organic phase is extracted twice with water. After drying over $MgSO_4$ the solvent is removed and the residue dried in vacuo.

Yield: 2.0 g (45% of theory), R_f value: 0.55 (silica gel, methylene chloride/methanol/ammonia=9:1:0.1) $C_{12}H_{17}N_3O_3$.

ESI mass spectrum: m/z=252 $[M+H^+]$.

The following compounds are prepared analogously to Example VI:

(1) 4-[N-(3-dimethylamino-propyl)-N-acetyl-amino]-nitrobenzene

Prepared from 4-(3-dimethylamino-propylamino)-nitrobenzene (according to Gabbay et al., J. Am. Chem. Soc. 91, 5136 (1969) and acetyl chloride

(2) 4-[N-(2-dimethylamino-ethyl)-N-propionyl-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and propionyl chloride

(3) 4-[N-acetyl-N-(dimethylaminocarbonylmethyl)-amino]-nitrobenzene

Prepared from 4-[N-(dimethylaminocarbonylmethyl)-amino]-nitrobenzene and acetyl chloride

(4) 4-[N-(2-dimethylamino-ethyl)-N-butyryl-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and butyryl chloride

(5) 4-[N-(2-dimethylamino-ethyl)-N-isobutyryl-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and isobutyryl chloride

(6) 4-[N-(2-dimethylamino-ethyl)-N-benzoyl-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and benzoyl chloride

(7) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-1,3-dinitrobenzene

Prepared from 4-(2-dimethylamino-ethyl-amino)-1,3-dinitrobenzene and acetyl chloride

(8) 4-[N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and furan-2-carbonyl chloride

(9) 4[-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and 2-methoxy-benzoyl chloride

(10) 4-[N-(2-dimethylamino-ethyl)N-(pyridine-3-carbonyl)-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and nicotinic acid chloride

(11) 4-[N-(2-dimethylamino-ethyl)-N-(phenyl-acetyl)-amino]-nitrobenzene

Prepared from 4-(2-dimethylamino-ethylamino)-nitrobenzene and phenylacetyl-chloride

(12) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-3-bromo-nitrobenzene

Prepared from 4-[N-(2-dimethylamino-ethyl)-amino]-3-bromo-nitrobenzene and acetyl chloride

(13) N-acryloyl-N-methyl-4-nitro-aniline

Prepared from 4-methylamino-nitrobenzene and acrylic acid chloride

(14) N-acryloyl-N-isopropyl-4-nitro-aniline

Prepared from 4-isopropylamino-nitrobenzene and acrylic acid chloride

(15) N-acryloyl-N-benzyl-4-nitro-aniline

Prepared from 4-benzylamino-nitrobenzene and acrylic acid chloride

(16) N-bromoacetyl-N-methyl-4-nitro-aniline

Prepared from 4-methylamino-nitrobenzene and bromoacetyl chloride

(17) N-bromoacetyl-N-isopropyl-4-nitro-aniline

Prepared from 4-isopropylamino-nitrobenzene and bromoacetyl chloride

(18) N-bromoacetyl-N-benzyl-4-nitro-aniline

Prepared from 4-benzylamino-nitrobenzene and bromoacetyl chloride

EXAMPLE VII

N-(dimethylaminomethylcarbonyl)-N-methyl-4-nitro-aniline

1.8 g of dimethylamine hydrochloride and 5.5 g of potassium carbonate are placed in 80 ml of acetone and 4.2 g of N-bromoacetyl-N-methyl-4nitroaniline are added in three batches at room temperature. The mixture is stirred for 12 hours at room temperature. After this time the mixture is filtered and the filtrate is evaporated down. The residue is dissolved in ethyl acetate, washed twice with water, dried over sodium sulphate and finally concentrated by rotary evaporation.

Yield: 2.8 g (79% of theory), R_f value: 0.5 (silica gel, ethyl acetate/methanol=7:3).

Meltingpoint: 121–122° C.

The following compounds are prepared analogously to Example VII:

(1) N-(piperidin-1-yl-methylcarbonyl)-N-methyl-4-nitroaniline

(2) N-(morpholin-4-yl-methylcarbonyl)-N-methyl-4-nitroaniline

(3) N-[(4-benzyl-piperazin-1-yl)-methylcarbonyl]-N-methyl-4-nitroaniline

(4) N-(pyrrolidin-1-yl-methylcarbonyl)-N-methyl-4-nitroaniline

(5) N-[(N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl]-N-methyl-4-nitroaniline

(6) N-[(N-benzyl-N-methyl-amino)-methylcarbonyl]-N-methyl-4-nitroaniline

(7) N-[di-(2-methoxyethyl)-amino-methylcarbonyl]-N-methyl-4-nitroaniline

(8) N-(dimethylaminomethylcarbonyl)-N-isopropyl-4-nitro-aniline

(9) N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-4-nitro-aniline

(10) N-[(4-tert.butoxycarbonyl-piperazin-1-yl) methylcarbonyl]-N-isopropyl-4-nitro-aniline

(11) N-[(N-benzyl-N-methyl-amino)-methylcarbonyl]-N-benzyl-4-nitro-aniline

(12) N-(dimethylaminomethylcarbonyl)-N-benzyl-4-nitro-aniline

(13) N-(piperidin-1-yl-methylcarbonyl)-N-benzyl-4-nitro-aniline

(14) N-[di-(2-hydroxyethyl)-amino-methylcarbonyl]-N-methyl-4-nitroaniline

(15) N-[(N-(2-methoxyethyl)-N-methyl-amino)-methylcarbonyl]-N-methyl-4-nitroaniline

(16) N-[(N-(2-dimethylamino-ethyl)-N-methyl-amino)-methylcarbonyl]-N-methyl-4-nitroaniline

(17) N-[(4-methyl-piperazin-1-yl)-methylcarbonyl]-N-methyl-4-nitroaniline

(18) N-[(imidazol-1-yl)-methylcarbonyl]-N-methyl-4-nitroaniline

(19) N-[(phthalimido-2-yl)-methylcarbonyl]-N-methyl-4-nitroaniline

EXAMPLE VIII

N-[(2-dimethylamino-ethyl)-carbonyl]-N-benzyl-4-nitro-aniline

0.5 g of dimethylamine hydrochloride, 1.1 ml of triethylamine and 1.2 g of N-acryloyl-N-benzyl-4-nitro-aniline are dissolved in 50 ml of methanol and stirred for 24 hours at room temperature. After this time the mixture is evaporated down. The residue is purified over an aluminium oxide column (activity 2–3) with methylene chloride/ethanol 50:1 as eluant.

Yield: 1.4 g (98% of theory), R_f value: 0.8 (aluminium oxide, methylene chloride/ethanol=20:1).

Melting point: 73° C.

The following compounds are prepared analogously to Example VIII:

(1) N-[(2-dimethylamino-ethyl)-carbonyl]-N-isopropyl-4-nitro-aniline

Prepared from N-acryloyl-N-isopropyl-4-nitro-aniline and dimethylamine hydrochloride

(2) N-[(2-dimethylamino-ethyl)-carbonyl]-N-methyl-4-nitro-aniline

Prepared from N-acryloyl-N-methyl-4-nitro-aniline and dimethylamine hydrochloride

(3) N-[(2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl]-N-methyl-4-nitro-aniline

Prepared from N-acryloyl-N-methyl-4-nitro-aniline and N-tert.butoxycarbonyl-piperazine

(4) N-[(2-(piperidin-1-yl)-ethyl)-carbonyl]-N-methyl-4-nitroaniline

Prepared from N-acryloyl-N-methyl-4-nitro-aniline and piperidine

(5) N-[(2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl]-N-methyl-4-nitro-aniline

Prepared from N-acryloyl-N-methyl-4-nitro-aniline and N-benzyl-N-methyl-amine

EXAMPLE IX

4-(4-methyl-piperazine-1-yl)-nitrobenzene

31.5 g of 4-chloro-1-nitrobenzene and 44.4 ml of 1-methylpiperazine are combined and stirred for 18 hours at 90° C. Then the solution is poured onto ice water and the precipitate formed is suction filtered, washed with water and recrystallised from ethanol/water 1:1. The residue is dried in vacuo at 75° C.

Yield: 44.0 g (99% of theory), R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1).

Melting point: 108–112° C.

The following compounds are prepared analogously to Example IX:

(1) N-(2-dimethylaminoethyl)-N-methyl-4-nitroaniline

Prepared from 1-fluoro-4-nitrobenzene and 1-dimethylamino-2-methylamino-ethane

(2) N-(3-dimethylaminopropyl)-N-methyl-4-nitroaniline

Prepared from 1-fluoro-4-nitrobenzene and 1-dimethylamino-3-methylamino-propane

(3) 4-(N-carboxymethyl-amino)-nitrobenzene

Prepared from 1-fluoro-4-nitrobenzene and glycine

(4) N-cyclohexyl-p-phenylenediamine

Prepared from 1-fluoro-4-nitrobenzene and cyclohexylamine

(5) 6-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-phthalimido-2-yl-nitrobenzene

Prepared from 2-nitro-4-phthalimido-2-yl-fluorobenzene, N-(2-dimethylamino-ethyl)-methanesulphonamide and sodium hydride as base

(6) 6[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-1,3-dinitrobenzene

Prepared from 2,4-dinitro-chlorobenzene, N-(2-dimethylamino-ethyl)-methanesulphonamide and sodium hydride as base

(7) 4-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-chloro-nitrobenzene

Prepared from 2-fluoro-5-nitro-chlorobenzene, N-(2-dimethylamino-ethyl)-methanesuiphonamide and sodium hydride as base

(8) 4-(2-dimethylamino-ethyl-amino)-1,3-dinitrobenzene

Prepared from 1-chloro-2,4-dinitro-benzene and N,N-dimethyl-ethylenediamine

(9) 4-[N-(2-dimethylamino-ethyl)-N-(ethylsulphonyl)-amino]-nitrobenzene

Prepared from 1-fluoro-4-nitro-benzene, N-(2-dimethylamino-ethyl)-ethanesulphonamide and sodium hydride as base

(10) 4-[N-(2-dimethylamino-ethyl)-N-(propylsulphonyl)-amino]-nitrobenzene

Prepared from 1-fluoro-4nitro-benzene, N-(2-dimethylamino-ethyl)-propanesulphonamide and sodium hydride as base

(11) 4-[N-(2-dimethylamino-ethyl)-N-(butylsulphonyl)-amino]-nitrobenzene

Prepared from 1-fluoro-4nitro-benzene, N-(2-dimethylamino-ethyl)-butanesulphonamide and sodium hydride as base

(12) 4-[N-(2-dimethylamino-ethyl)-N-(benzylsulphonyl)-amino]-nitrobenzene

Prepared from 1-fluoro-4nitro-benzene, N-(2-dimethylamino-ethyl)-C-phenylmethanesulphonamide and sodium hydride as base

(13) 4-[N-(2-dimethylamino-ethyl)-N-(phenylsulphonyl)-amino]-nitrobenzene

Prepared from 1-fluoro-4-nitro-benzene, N-(2-dimethylamino-ethyl)-benzenesulphonamide and sodium hydride as base

(14) 4-[N-(2-dimethylamino-ethyl)-N-(isopropylsulphonyl)-amino]-nitrobenzene

Prepared from 1-fluoro-4-nitro-benzene, N-(2-dimethylamino-ethyl)-isopropylsulphonamide and sodium hydride as base

(15) 4-[N-(2-dimethylamino-ethyl)-amino]-3-bromo-nitrobenzene

Prepared from 2-bromo-1-fluoro-4-nitro-benzene and N,N-dimethyl-ethylenediamine

(16) 4-isopropylamino-nitrobenzene

Prepared from 1-fluoro-4-nitrobenzene and isopropylamine

(17) 4-benzylamino-nitrobenzene

Prepared from 1-fluoro-4-nitrobenzene and benzylamine

EXAMPLE X

4-(imidazol-4-yl)-nitrobenzene

9.5 g of 2-phenylimidazole are carefully dissolved in 50 ml of concentrated sulphuric acid and 5.8 g of ammonium nitrate are added to this solution at 0° C. After a further 60 minutes stirring at 0° C. the mixture is poured onto ice water, made basic with ammonia water and the precipitate formed is suction filtered and recrystallised from ethanol.

Yield: 8.0 g (64% of theory), R_f value: 0.6 (silica gel, ethyl acetate/ethanol=10:1) $C_9H_7N_3O_2$.

Mass spectrum: m/z=189 [M^+].

The following compounds are prepared analogously to Example X:

(1) 4-(imidazol-2-yl)-nitrobenzene

Prepared from 4-(imidazol-2-yl)-benzene

(2) 4-(5-methyl-imidazol-4-yl)-nitrobenzene

Prepared from 4-methyl-5-phenyl-imidazole (J. Heterocycl. Chem. 1983, 20, 1277–1281)

EXAMPLE XI

4-(2-(imidazol-4-yl)-ethylene)-nitrobenzene

1.5 g of 4-nitrobenzaldehyde and 7.45 g of (N-trityl-imidazol-4-yl-methyl)-triphenylphosphonium chloride are dissolved in 75 ml of tetrahydrofuran and to this solution 3.0 ml of DBU are added dropwise at room temperature. After a further 120 minutes stirring at room temperature the mixture is poured onto water and the precipitate formed is suction filtered. The product is taken up in 25 ml of 1N hydrochloric acid and refluxed for 4 hours. After this time it is neutralised with ammoniacal water, extracted with ethyl acetate and the organic phase is washed with water, dried over sodium sulphate and evaporated down. The residue is purified over a silica gel column with methylene chloride/methanol 10:1 as eluant.

Yield: 1.0 g of (47% of theory), R_f value: 0.6 (silica gel, ethyl acetate/ethanol=10:1).

Melting point: 185–188° C.

EXAMPLE XII

4-(piperidin-1-yl-methyl)-nitrobenzene

40.0 g of 4-nitrobenzyl bromide are dissolved in 500 ml of methylene chloride, 51.5 ml of triethylamine are added and 18.3 ml of piperidine are carefully added dropwise. After the end of the exothermic reaction the mixture is refluxed for another 30 minutes. After cooling it is washed with water and the organic phase is dried over sodium sulphate. Finally, the organic phase is evaporated down.

Yield: 36.3 g of (89% of theory), R_f value: 0.6 (silica gel, methylene chloride/methanol=9:1) $C_{12}H_{16}N_2O_2$.

Mass spectrum: m/z=221 [M^+].

The following compounds are prepared analogously to Example XII:

(1) 4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-nitrobenzene

(2) 3-(N,N-dimethyl-aminomethyl)-nitrobenzene

(3) 4-(N,N-dimethyl-aminomethyl)-nitrobenzene

(4) 4-(2-dimethylamino-ethyl)-nitrobenzene

(5) 4-(2-diethylamino-ethyl)-nitrobenzene

(6) 4-(diethylamino-methyl)-nitrobenzene

(7) 4-(N-benzyl-N-methyl-aminomethyl)-nitrobenzene

(8) 4-(N-ethyl-N-methyl-aminomethyl)-nitrobenzene

(9) 4-[N-(n-hexyl)-N-methyl-aminomethyl]-nitrobenzene

(10) 4-(thiomorpholin-4-yl-methyl)-nitrobenzene

(11) 4-[(4-methyl-piperazine-1-yl)-methyl]-nitrobenzene

(12) 4-(imidazol-1-yl-methyl)-nitrobenzene

(13) 4-[2-(4-hydroxy-piperidin-1-yl)-ethyl-amino]-nitrobenzene

(14) 4-[(3-hydroxy-pyrrolidin-1-yl)-methyl]-nitrobenzene

(15) 4-(1,2,4-triazol-1-yl-methyl)-nitrobenzene

(16) 4-(1,2,3-triazol-2-yl-methyl)-nitrobenzene

(17) 4-(1,2,3-triazol-1-yl-methyl)-nitrobenzene

(18) 4-[(N-ethoxycarbonylmethyl-N-methyl-amino)-methyl]-nitrobenzene

(19) 4-[(N-aminocarbonytmethyl-N-methyl-amino)-methyl]-nitrobenzene

(20) 4-(azetidin-1-yl-methyl)-nitrobenzene

(21) 4-[(di-(2-methoxy-ethyl)-amino)-methyl]-nitrobenzene

(22) 4-[N-(N-tert.butoxycarbonyl-3-amino-propyl)-N-methyl-aminomethyl]-nitrobenzene

(23) 4-[(N-propyl-N-methyl-amino)-methyl]-nitrobenzene

(24) 4-[(N-(2-dimethylamino-ethyl)-N-methyl-amino)-methyl]-nitrobenzene

(25) 4-[(N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl]-nitrobenzene

(26) 4-[(N-(2-methoxy-ethyl)-N-methyl-amino)-methyl]-nitrobenzene

(27) 4-[(N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl]-nitrobenzene

(28) 4-[(N-(dioxolan-2-yl-methyl)-N-methyl-amino)-methyl]-nitrobenzene

(29) 4-(3-oxo-piperazine-1-yl-methyl)-nitrobenzene

EXAMPLE XIII

4-[(N-carboxymethyl-N-methyl-amino)-methyl]-nitrobenzene

7.33 g of 4-[(N-ethoxycarbonylmethyl-N-methyl-amino)-methyl]-nitrobenzene are dissolved in 140 ml of ethanol, 34.0 ml of 1N sodium hydroxide solution are added and the mixture is stirred for half an hour at room temperature. After this time the mixture is neutralised with 34 ml of 1N hydrochloric acid, the solvent removed, the residue taken up in methylene chloride and extracted with water. The aqueous phase is evaporated down and the residue is recrystallised from methylene chloride.

Yield: 5.43 g (84% of theory), R_f value: 0.4 (silica gel, methylene chloride/methanol=2:1) $C_{10}OH_{12}N_2O_4$.

Mass spectrum: m/z=223 [M^+].

EXAMPLE XIV

4-(N-ethyl-aminomethyl)-nitrobenzene

6.0 g of 4-nitrobenzyl bromide are dissolved in 25 ml of ethanol, combined with 25 ml of 10% ethanolic ethylamine solution and refluxed for 2 hours. Then the solution is concentrated by rotary evaporation, the residue is taken up with methylene chloride and washed with dilute sodium hydroxide solution. Finally the organic phase is evaporated down.

Yield: 2.3 g (46% of theory), R_f value: 0.2 (silica gel, methylene chloride/methanol=9:1) $C_9H_{12}N_2O_2$.

ESI mass spectrum: m/z=179 [$M-H^-$].

The following compounds are prepared analogously to Example XIV:

(1) 4-[N-(4-chlorobenzyl)-aminomethyl]-nitrobenzene

(2) 4-(N-cyclohexyl-aminomethyl)-nitrobenzene

(3) 4-(N-isopropyl-aminomethyl)-nitrobenzene

(4) 4-(N-propyl-aminomethyl)-nitrobenzene

(5) 4-(N-methyl-aminomethyl)-nitrobenzene

(6) 4-(N-butyl-aminomethyl)-nitrobenzene

(7) 4-(N-methoxycarbonylmethyl-aminomethyl)-nitrobenzene

(8) 4-(N-benzyt-aminomethyl)-nitrobenzene

(9) 4-(aminomethyl)-nitrobenzene

(10) 4-(pyrrolidin-1-yl-methyl)-nitrobenzene

(11) 4-(morpholin-4-yl-methyl)-nitrobenzene

(12) 4-(hexamethyleneiminomethyl)-nitrobenzene

(13) 4-(4-hydroxy-piperidin-1-yl-methyl)-nitrobenzene

(14) 4-(4-methoxy-piperidin-1-yl-methyl)-nitrobenzene

(15) 4-(4-methyl-piperidin-1-yl-methyl)-nitrobenzene

(16) 4-(4-ethyl-piperidin-1-yl-methyl)-nitrobenzene

(17) 4-(4-isopropyl-piperidin-1-yl-methyl)-nitrobenzene

(18) 4-(4-phenyl-piperidin-1-yl-methyl)-nitrobenzene

(19) 4-(4-benzyl-piperidin-1-yl-methyl)-nitrobenzene

(20) 4-(4-ethoxycarbonyl-piperidin-1-yl-methyl)-nitrobenzene

(21) 4-(N,N-dipropyl-aminomethyl)-nitrobenzene

(22) 4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-nitrobenzene

(23) 4-(2-morpholin-4-yl-ethyl)-nitrobenzene

(24) 4-(2-pyrrolidin-1-yl-ethyl)-nitrobenzene

(25) 4-(2-piperidin-1-yl-ethyl)-nitrobenzene

(26) 4-(N-ethyl-N-benzyl-aminomethyl)-nitrobenzene

(27) 4-(N-propyl-N-benzyl-aminomethyl)-nitrobenzene

(28) 4[N-methyl-N-(4-chlorobenzyl)-aminomethyl]-nitrobenzene

(29) 4-[N-methyl-N-(4-bromobenzyl)-aminomethyl]-nitrobenzene

(30) 4[N-methyl-N-(4-fluorobenzyl)-aminomethyl]-nitrobenzene

(31) 4-[N-methyl-N-(4-methylbenzyl)-aminomethyl]-nitrobenzene

(32) 4-[N-methyl-N-(3-chlorobenzyl)-aminomethyl]-nitrobenzene

(33) 4-[N-methyl-N-(3,4-dimethoxybenzyl)-aminomethyl]-nitrobenzene

(34) 4-[N-methyl-N-(4-methoxybenzyl)-aminomethyl]-nitrobenzene

(35) 4-(N-2,2,2-trifluoroethyl-N-benzyl-aminomethyl)-nitrobenzene

(36) 4-[N-2,2,2-trifluoroethyl-N4-chlorobenzyl)-aminomethyl]-nitrobenzene

(37) 4-(thiomorpholin-4-yl-methyl)-nitrobenzene

(38) 4-(azetidion-1-yl-methyl)-nitrobenzene

(39) 4-(3,4-dihydropyrrolidin-1-yl-methyl)-nitrobenzene

(40) 4-(3,4-dihydropiperidin-1-yl-methyl)-nitrobenzene

(41) 4-(2-methoxycarbonyl-pyrrolidin-1-yl-methyl)-nitrobenzene

(42) 4-(3,5-dimethyl-piperidin-1-yl-methyl)-nitrobenzene

(43) 4-(4-phenyl-piperazin-1-yl-methyl)-nitrobenzene

(44) 4-(4-phenyl-4-hydroxy-piperidin-1-yl-methyl)-nitrobenzene

(45) 4-[N-(3,4,5-trimethoxybenzyl-N-methyl-aminomethyl)-nitrobenzene

(46) 4-[N-(3,4-dimethoxybenzyl)-N-ethyl-aminomethyl]-nitrobenzene

(47) 4-[N-(2,6-dichlorobenzyl)-N-methyl)-aminomethyl]-nitrobenzene

(48) 4-[N-(4-trifluoromethylbenzyl)-N-methyl)-aminomethyl]-nitrobenzene

(49) 4-(N-benzyl-N-isopropyl-aminomethyl)-nitrobenzene

(50) 4-(N-benzyl-N-tert.butyl-aminomethyl)-nitrobenzene

(51) 4-(N,N-diisopropyl-aminomethyl)-nitrobenzene

(52) 4-(N,N-diisobutyl-aminomethyl)-nitrobenzene

(53) 4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

(54) 4-(2,3-dihydro-isoindol-2-yl-methyl)-nitrobenzene

(55) 4-(6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(56) 4-(1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(57) 4-[N-(2-hydroxyethyl)-N-benzyl-aminomethyl]-nitrobenzene

(58) 4-[N-(1-ethyl-pentyl)-N-(pyridin-2-yl-methyl)-aminomethyl]-nitrobenzene

(59) 4-(piperin-1-yl-methyl)-1,3-dinitrobenzene

(60) 4-(N-phenethyl-N-methyl-aminomethyl)-nitrobenzene

(61) 4-[N-(3,4-dihydroxy-phenethyl)-N-methyl-aminomethyl]-nitrobenzene

(62) 4-[N-(3,4,5-trimethoxy-phenethyl)-N-methyl-aminomethyl]-nitrobenzene

(63) 4-[N-(3,4-dimethoxy-phenethyl)-N-methyl-aminomethyl]-nitrobenzene

(64) 4-[N-(3,4-dimethoxy-benzyl)-N-methyl-aminomethyl]-nitrobenzene

(65) 4-[N-(4-chloro-benzyl)-N-methyl-aminomethyl]-nitrobenzene

(66) 4-[N-(4-bromo-benzyl)-N-methyl-aminomethyl]-nitrobenzene

(67) 4-[N-(4-fluoro-benzyl)-N-methyl-aminomethyl]-nitrobenzene

(68) 4-[N-(4-methyl-benzyl)-N-methyl-aminomethyl]-nitrobenzene

(69) 4-[N-(4-nitro-phenethyl)-N-methyl-aminomethyl]-nitrobenzene

(70) 4-(N-phenethyl-N-benzyl-aminomethyl)-nitrobenzene

(71) 4-(N-phenethyl-N-cyclohexyl-aminomethyl)-nitrobenzene

(72) 4-[N-(2-(pyridin-2-yl)-ethyl)-N-methyl-aminomethyl]-nitrobenzene

(73) 4-[N-(2-(pyridin-4-yl)-ethyl)-N-methyl-aminomethyl]-nitrobenzene

(74) 4-[N-(pyridin-4-yl-methyl)-N-methyl-aminomethyl]-nitrobenzene

(75) 4-(N,N-dibenzyl-aminomethyl)-nitrobenzene

(76) 4-[N-(4-nitro-phenethyl)-N-propyl-aminomethyl]-nitrobenzene

(77) 4-(N-benzyl-N-(3-cyano-propyl)-aminomethyl)-nitrobenzene

(78) 4-(N-benzyl-N-allyl-aminomethyl)-nitrobenzene

(79) 4-[N-benzyl-N-(2,2,2-trifluoroethyl)-aminomethyl]-nitrobenzene

(80) 4-[N-(2-benzo(1,3)dioxol-5-yl-methyl)-N-methyl-aminomethyl]-nitrobenzene

(81) 4-(7-chloro-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

(82) 4-(7,8-dichloro-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

(83) 4-(7-methoxy-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

(84) 4-(7-methyl-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-nitrobenzene

(85) 4-(7,8-dimethoxy-2,3,4,5-tetrahydro-benzo(d) azepin-3-yl-methyl)-nitrobenzene

(86) 4-(6,7-dichloro-1,2,3 ,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(87) 4-(6,7-dimethyl-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(88) 4-(6-chloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(89) 4-(7-chloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(90) 4-(6-methoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(91) 4-(7-methoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-nitrobenzene

(92) 4-[(2,3,4,5-tetrahydro-azepino(4,5-b)pyrazin-3-yl)-methyl]-nitrobenzene

(93) 4-[(7-amino-2,3,4,5-tetrahydro-azepino(4,5-b) pyrazin-3-yl)-methyl]-nitrobenzene

(94) 4-[(2-amino-5,6,7,8-tetrahydro-azepino(4,5-d) thiazol-6-yl)-methyl]-nitrobenzene

(95) 4-[(5,6,7,8-tetrahydro-azepino(4,5-d)thiazol-6-yl)-methyl]-nitrobenzene

EXAMPLE XV

4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-nitrobenzene

6.0 g of 4-(thiomorpholin-4-yl-methyl)-nitrobenzene are dissolved in 100 ml of methylene chloride and 10.3 g of

meta-chloroperbenzoic acid are slowly added. After a further 3 hours stirring at room temperature the precipitate obtained is filtered off.

Yield: 6.2 g (91% of theory) R_f value: 0.5 (silica gel, methylene chloride/methanol=1:1) $C_{11}H_{14}N_2O_4S$.

Mass spectrum: n/z=270 [M^+].

The following compound is prepared analogously to Example XV:

(1) 4-(1-oxo-thiomorpholin-4-yl-methyl)-nitrobenzene

EXAMPLE XVI

4-[N-(3-amino-propyl)-N-methylsulphonyl-amino]-nitrobenzene

9.5 g of 4-[N-(3-phthalimido-2-yl-propyl)-N-methylsulphonyl-amino]-nitrobenzene are dissolved in 200 ml of ethanol, 11.5 ml of hydrazine hydrate are added and the mixture is stirred for 1.5 hours at 50° C. After cooling the residue is largely evaporated down, water is added and the solution is extracted with methylene chloride. The organic phase is dried, evaporated down and purified over a silica gel column with methylene chloride/methanol/ammonia 9:1:0.1.

Yield: 2.5 g (39% of theory) R_f value: 0.2 (silica gel, methylene chloride/methanol=9:1) $C_{10}H_{15}N_3O_4S$.

ESI mass spectrum: m/z=272 [$M-H^-$].

The following compound is prepared analogously to Example XVI:

(1) 6[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-amino-nitrobenzene

Prepared from 6-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-phthalimido-2-yl-nitrobenzene

EXAMPLE XVII

4-(1-methyl-imidazol-2-yl)-nitrobenzene

7.5 g of 4-(imidazol-2-yl)-nitrobenzene are dissolved in 50 ml of dimethylsulphoxide and at 0° C. 5.0 g of potassium tert.butoxide are added. After one hour of stirring at room temperature 2.6 ml of methyl iodide are added dropwise and the mixture is stirred for one hour at room temperature. After this time the residue is poured onto ice water and the precipitate formed is suction filtered, washed with water and dried.

Yield: 6.1 g (76% of theory), R_f value: 0.6 (silica gel, methylene chloride/methanol=10:1)

Melting point: 186–187° C.

The following compounds are prepared analogously to Example XVII:

(1) 4-(1-ethyl-imidazol-2-yl)-nitrobenzene

Prepared from 4-(imidazol-2-yl)-nitrobenzene and ethyl iodide

(2) 4-(1-benzyl-imidazol-2-yl)-nitrobenzene

Prepared from 4-(imidazol-2-yl)-nitrobenzene and benzyl bromide

EXAMPLE XVIII

4-[(N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl]-nitrobenzene

5.0 g of 4-methylaminomethyl-nitrobenzene are dissolved in 30 ml of dimethylformamide and 4.6 g of 2-(2-methoxy-ethoxy)-ethyl chloride are added. After six hours' stirring at 100° C. the solvent is removed and the residue is taken up in ethyl acetate. The organic phase is washed with water and dried over sodium sulphate. After the elimination of the solvent the residue is purified over an aluminium oxide column (activity 2-3) with toluene/ethyl acetate 5:1 as eluant.

Yield: 2.3 g (29% of theory) R_f value: 0.5 (aluminium oxide, toluene/ethyl acetate 5:1) $C_{13}H_{20}N_2O_4$.

ESI mass spectrum: m/z=267 [$M-H^-$].

EXAMPLE XIX

4-(N-ethyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

2.2 g of 4-(ethylaminomethyl)-nitrobenzene are dissolved in 50 ml of ethyl acetate and stirred with 2.6 g of di-tert-butyl. dicarbonate (tert.butoxycarbonyl-anhydride) for 30 minutes at room temperature. Then the solution is washed with water and evaporated down.

Yield: 3.4 g of theory R_f value: 0.3 (silica gel, methylene chloride/methanol=50:1).

Melting point: 85° C.

The following compounds are prepared analogously to Example XIX:

(1) 4-[N-(4-chlorophenyl-methyl)-N-tert.butoxycarbonyl-aminomethyl]-nitrobenzene

(2) 4-(N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(3) 4-(N-cyclohexyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(4) 4-(N-isopropyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(5) (N-methyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(6) (4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(7) (N-butyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(8) (N-methoxycarbonylmethyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(9) 4-(N-benzyl-N-tert.butoxycarbonyl-aminomethyl)-nitrobenzene

(10) 4-[N-(3-trifluoroacetylamino-propyl)-N-methylsulphonyl-amino]-nitrobenzene

Prepared from 4-[N-(3-amino-propyl)-N-methylsulphonyl-amino]-nitrobenzene and trifluoroacetic acid anhydride

(11) 4-[(4-tert.butoxycarbonyl-piperazin-1-yl)-methyl]-nitrobenzene

EXAMPLE XX

4-(piperidin-1-yl-methyl)-aniline

37.0 g of 4-(piperidin-1-yl-methyl)-nitrobenzene are dissolved in 300 ml of methanol, 8.0 g of Raney nickel are added and the mixture is hydrogenated for 85 minutes with 3 bars of hydrogen at room temperature. The catalyst is filtered off and the filtrate is evaporated down.

Yield: 24.0 g (75% of theory), R_f value: 0.4 (silica gel, methylene chloride/methanol=9:1) $C_{12}H_{18}N_2$.

ESI mass spectrum: m/z=191 [$M+H^+$].

The following compounds are prepared analogously to Example VIII:

(1) 4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-aniline

(2) N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylenediamine

(3) 3dimethylaminomethyl)-aniline

(4) 4-(dimethylaminomethyl)-aniline

(5) 4-(2-dimethylamino-ethyl)-aniline

(6) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-aniline

(7) 4-[N-(3-dimethylamino-propyl)-N-acetyl-amino]-aniline

(8) 4-[N-(2-dimethylamino-ethyl)-N-benzoyl-amino]-aniline

(9) 4-[N-(2-dimethylamino-ethyl)-N-propionyl-amino]-aniline

(10) 4-[N-(2-dimethylamino-ethyl)-N-butyryl-amino]-aniline

(11) 4-[N-(2-dimethylamino-ethyl)-N-isobutyryl-amino]-aniline

(12) 4-(N-tert.butoxycarbonyl-aminomethyl)-aniline

(13) 4-(N-ethyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(14) 4-[N-(4-chlorophenyl-methyl)-N-tert.butoxycarbonyl-aminomethyl]-aniline

(15) 4-(N-cyclohexyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(16) 4-(N-isopropyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(17) 4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(18) 4-(N-methyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(19) 4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(20) 4-(N-methoxycarbonyl-methyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(21) 4-(N-benzyl-N-tert.butoxycarbonyl-aminomethyl)-aniline

(22) 4-(pyrrolidin-1-yl-methyl)-aniline

(23) 4-(morpholin-4-yl-methyl)-aniline

(24) 4-(hexamethyleneiminomethyl)-aniline

(25) 4-(4-hydroxy-piperidin-1-yl-methyl)-aniline

(26) 4-(4-methoxy-piperidin-1-yl-methyl)-aniline

(27) 4-(4-methyl-piperidin-1-yl-methyl)-aniline

(28) 4-(4-ethyl-piperidin-1-yl-methyl)-aniline

(29) 4-(4-isopropyl-piperidin-1-yl-methyl)-aniline

(30) 4-(4-phenyl-piperidin-1-yl-methyl)-aniline

(31) 4-(4-benzyl-piperidin-1-yl-methyl)-aniline

(32) 4-(4-ethoxycarbonyl-piperidin-1-yl-methyl)-aniline

(33) 4-(N,N-dipropyl-aminomethyl)-aniline

(34) 4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-aniline

(35) 4-(2-morpholin-4-yl-ethyl)-aniline

(36) 4-(2-pyrrolidin-1-yl-ethyl)-aniline

(37) 4-(2-piperidin-1-yl-ethyl)-aniline

(38) 4-(N-propyl-N-benzyl-aminomethyl)-aniline

(39) 4-[N-(n-bexyl)-N-methyl-aminomethyl]-aniline

(40) 4-[N-methyl-N-(4-chlorobenzyl)-aminomethyl]-aniline

(41) 4-[N-methyl-N-(4-bromobenzyl)-aminomethyl]-aniline

(42) 4-[N-methyl-N-(4-methylbenzyl)-aminomethyl]-aniline

(43) 4-[N-methyl-N-(4-fluorobenzyl)-aminomethyl]-aniline

(44) 4-[N-methyl-N-(3-chlorobenzyl)-aminomethyl]-aniline

(45) 4-[N-methyl-N-(3,4-dimethoxybenzyl)-aminomethyl]-aniline

(46) 4-[N-methyl-N-(4-methoxybenzyl)-aminomethyl]-aniline

(47) 4-(N-2,2,2-trifluoroethyl-N-benzyl-aminomethyl) aniline

(48) 4-[N-2,2,2-trifluoroethyl-N-(4-chlorobenzyl)-aminomethyl]-aniline

(49) 4-(thiomorpholin-4-yl-methyl)-aniline

(50) 4-(1-oxo-thiomorpholin-4-yl-methyl)-aniline

(51) 4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-aniline

(52) 4-(azetidion-1-yl-methyl)-aniline

(53) 4-(3,4-dihydropyrrolidin-1-yl-methyl)-aniline

(54) 4-(3,4-dihydropiperidin-1-yl-methyl)-aniline

(55) 4-(2-methoxycarbonyl-pyrrolidin-1-yl-methyl)-aniline

(56) 4-(3,5-dimethyl-piperidin-1-yl-methyl)-aniline

(57) 4-(4-phenyl-piperazin-1-yl-methyl)aniline

(58) 4-(4-phenyl-4-hydroxy-piperidin-1-yl-methyl)-aniline

(59) 4-[N-(3,4,5-trimethoxy-benzyl)-N-methyl-aminomethyl]-aniline

(60) 4-[N-(3,4-dimethoxy-benzyl)-N-ethyl-aminomethyl]-aniline

(61) 4-(N-benzyl-N-ethyl-aminomethyl)-aniline

(62) 4-[N-(2,6-dichlorobenzyl)-N-methyl-aminomethyl]-aniline

(63) 4-[N-(4-trifluoromethylbenzyl)-N-methyl-aminomethyl]-aniline

(64) 4N-benzyl-N-isopropyl-aminomethyl)-aniline

(65) 4N-benzyl-N-tert.butyl-aminomethyl)-aniline

(66) 4diethylamino-methyl)-aniline

(67) 4-(2-diethylamino-ethyl)-aniline

(68) 4-(N,N-diisopropyl-aminomethyl)-aniline

(69) 4-(N,N-diisobutyl-aminomethyl)-aniline

(70) 4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

(71) 4-(2,3-dihydro-isoindol-2-yl-methyl)-aniline

(72) 4-(6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(73) 4-(1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(74) 4-[N-(2-hydroxy-ethyl)-N-benzyl-aminomethyl]-aniline

(75) 4-[N-(1-ethyl-pentyl)-N-(pyridin-2-yl-methyl)-aminomethyl]-aniline

(76) 4-(piperidin-1-yl-methyl)-3-nitro-aniline

(77) 4-(piperidin-1-yl-methyl)-3-amino-aniline

(78) 4-(N-benzyl-N-methyl-aminomethyl)-aniline

(79) 4-(N-ethyl-N-methyl-aminomethyl)-aniline

(80) 4-(N-phenethyl-N-methyl-aminomethyl)-aniline

(81) 4-[N-(3,4-dihydroxy-phenethyl)-N-methyl-aminomethyl]-aniline

(82) 4-[N-(3,4,5-trimethoxy-phenethyl)-N-methyl-aminomethyl]-aniline

(83) 4-[N-(3,4-dimethoxy-phenethyl)-N-methyl-aminomethyl]-aniline

(84) 4-[N-(3,4-dimethoxy-benzyl)-N-methyl-aminomethyl]-aniline

(85) 4-[N-(4-chloro-benzyl)-N-methyl-aminomethyl]-aniline

(86) 4-[N-(4-bromo-benzyl)-N-methyl-aminomethyl]-aniline

(87) 4-[N-(4-fluoro-benzyl)-N-methyl-aminomethyl]-aniline

(88) 4-[N-(4-methyl-benzyl)-N-methyl-aminomethyl]-aniline

(89) 4-[N-(4-nitro-phenethyl)-N-methyl-aminomethyl]-aniline

(90) 4-(N-phenethyl-N-benzyl-aminomethyl)-aniline

(91) 4-(N-phenethyl-N-cyclohexyl-aminomethyl)-aniline

(92) 4-[N-(2-(pyridin-2-yl)-ethyl)-N-methyl-aminomethyl]-aniline

(93) 4-[N-(2-(pyridin-4-yl)-ethyl)-N-methyl-aminomethyl]-aniline

(94) 4-[N-(pyridin-4-yl-methyl)-N-methyl-aminomethyl]-aniline

(95) 4-(N,N-dibenzylaminomethyl)-aniline

(96) 4-[N-(4-nitro-benzyl)-N-propyl-aminomethyl]-aniline

(97) 4-[N-benzyl-N-(3-cyano-propyl)-aminomethyl]-aniline

(98) 4-(N-benzyl-N-allyl-aminomethyl)-aniline

(99) 4-[N-benzyl-N-(2,2,2-trifluoroethyl)-aminomethyl]-aniline

(100) 4-[(benzo(1,3)dioxol-5-yl-methyl)-methyl-aminomethyl]-aniline

(101) 4-(7-chloro-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

(102) 4-(7,8-dichloro-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

(103) 4-(7-methoxy-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

(104) 4-(7-methyl-2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-aniline

(105) 4-(7,8-dimethoxy-2,3,4,5-tetrahydro-benzo(d) azepin-3-yl-methyl)-aniline

(106) 4-(6,7-dichloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(107) 4-(6,7-dimethyl-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(108) 4-(6-chloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(109) 4-(7-chloro-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(110) 4-(6-methoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(111) 4-(7-methoxy-1,2,3,4-tetrahydro-isoquinolin-2-yl-methyl)-aniline

(112) 4-(2,3,4,5-tetrahydro-azepino(4,5-b)pyrazin-3-yl-methyl)-aniline

(113) 4-(7-amino-2,3,4,5-tetrahydro-azepino(4,5-b) pyrazin-3-yl-methyl)-aniline

(114) 4-(2-amino-5,6,7,8-tetrahydro-azepino(4,5-d) thiazol-6-yl-methyl)-aniline

(115) 4-(5,6,7,8-tetrahydro-azepino(4,5-d)thiazol-6-yl-methyl)-aniline

(116) 4-(4-methyl-piperazin-1-yl)-aniline

(117) 4-[N-(2-dimethylamino-ethyl)-N-methyl-amino]-aniline

(118) 4-[N-(3-dimethylamino-propyl)-N-methyl-amino]-aniline

(119) N-(3-dimethylamino-propyl)-N-methylsulphonyl-p-phenylenediamine

(120) 4-[(N-dimethylaminocarbonylmethyl-N-methylsulphonyl)-amino]-aniline

(121) N-(4-aminophenyl)-N-methyl-methanesulphonamide

(122) 4-(imidazol-4-yl)-aniline

(123) 4-(tetrazol-5-yl)-aniline

(124) 4-[N-(2-dimethylamino-ethyl)-N-propionyl-amino]-aniline

(125) N-(dimethylaminomethylcarbonyl)-N-methyl-p-phenylenediamine

(126) N-[(2-dimethylamino-ethyl)-carbonyl]-N-methyl-p-phenylenediamine

(127) 4-(N-acetyl-N-dimethylaminocarbonylmethyl)-amino)-aniline

(128) N-methylaminocarbonylmethyl-N-methylsulphonyl-p-phenylenediamine

(129) N-aminocarbonylmethyl-N-methylsulphonyl-p-phenylenediamine

(130) 4-(imidazolidin-2,4-dion-5-ylidene-methyl)-aniline

(131) 4-(imidazolidin-2,4-dion-5-yl-methyl)-aniline

(132) 4-(2-oxo-pyrrolidin-1-yl-methyl)-aniline

(133) N-cyanomethyl-N-methylsulphonyl-p-phenylenediamine

(134) 4-[2-(imidazol-4-yl)-ethyl]-aniline

(135) 4-[(4-methyl-piperazin-1-yl)-methyl]-aniline

(136) 4-[N-(2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino]-aniline

(137) 4-[N-(3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino]-aniline

(138) N-cyclohexyl-p-phenylenediamine

(139) 4-(pyridin-4-yl-methyl)-aniline

(140) 4-(imidazol-1-yl-methyl)-aniline

(141) 4-benzyl-aniline

(142) N-(3-trifluoroacetylamino-propyl)-N-methylsulphonyl-p-phenylenediamine

(143) tert.butyl 4-amino-phenylacetate

(144) 4-(imidazol-2-yl)-aniline

(145) 4-(1-methyl-imidazol-2-yl)-aniline

(146) 4-(1-ethyl-imidazol-2-yl)-aniline

(147) 4-(1-benzyl-imidazol-2-yl)-aniline

(148) 4-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-amino-aniline

(149) 4-[N-(2dimethylamino-ethyl)-N-methylsulphonyl-amino]-3-chloro-aniline

(150) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-3-amino-aniline

(151) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-3-bromo-aniline

(152) 4-[2-(4-hydroxy-piperidin-1-yl)-ethyl-amino]-aniline

(153) N-(2-dimethylamino-ethyl)-N-ethylsulphonyl-p-phenylenediamine

(154) N-(2-dimethylamino-ethyl)-N-propylsulphonyl-p-phenylenediamine

(155) N-(2-dimethylamino-ethyl)-N-isopropylsulphonyl-p-phenylenediamine

(156) N-(2-dimethylamino-ethyl)-N-butylsulphonyl-p-phenylenediamine

(157) N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-p-phenylenediamine

(158) N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-p-phenylenediamine

(159) 4-((3-hydroxy-pyrrolidin-1-yl)-methyl)-aniline

(160) 4-[N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino]-aniline

(161) 4-[N-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino]-aniline

(162) 4-[N-(2-dimethylamino-ethyl)-N-(pyridine-3-carbonyl)-amino]-aniline

(163) 4-[N-(2-dimethylamino-ethyl)-N-(phenyl-acetyl)-amino]-aniline

(164) N-(piperidin-1-yl-methylcarbonyl)-N-methyl-p-phenylenediamine

(165) N-(morpholin-4-yl-methylcarbonyl)-N-methyl-p-phenylenediamine

(166) N-[(4-benzyl-piperazin-1-yl)-methylcarbonyl]-N-methyl-p-phenylenediamine

(167) N-(pyrrolidin-1-yl-methylcarbonyl)-N-methyl-p-phenylenediamine

(168) 4-(5-methyl-imidazol-4-yl)-aniline

(169) N-[(2-dimethylamino-ethyl)-carbonyl]-N-isopropyl-p-phenylenediamine

(170) N-[(2-dimethylamino-ethyl)-carbonyl]-N-benzyl-p-phenylenediamine

(171) N-(N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-p-phenylenediamine

(172) N-[(N-benzyl-N-methyl-amino)-methylcarbonyl]-N-methyl-p-phenylenediamine

(173) N-[di-(2-methoxyethyl)-amino-methylcarbonyl]-N-methyl-p-phenylenediamine

(174) N-[(2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl]-N-methyl-p-phenylenediamine

(175) N-[(2-(piperidin-1-yl)-ethyl)-carbonyl]-N-methyl-p-phenylenediamine

(176) N-[(2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl]-N-methyl-p-phenylenediamine

(177) N-(dimethylaminomethylcarbonyl)-N-isopropyl-p-phenylenediamine

(178) N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-p-phenylenediamine

(179) N-[(4-tert.butoxycarbonyl-piperazin-1-yl)-methylcaronyl]-N-isopropyl-p-phenylenediamine

(180) N-[(N-benzyl-N-methyl-amino)-methylcarbonyl]-N-benzyl-p-phenylenediamine

(181) N-(dimethylaminomethylcarbonyl)-N-benzyl-p-phenylenediamine

(182) N-(piperidin-1-yl-methylcarbonyl)-N-benzyl-p-phenylenediamine

(183) 4-(1,2,4-triazol-1-yl-methyl)-aniline

(184) 4-(1,2,3-triazol-2-yl-methyl)-aniline

(185) 4-(1,2,3-triazol-1-yl-methyl)-aniline

(186) 4-[(N-ethoxycarbonylmethyl-N-methyl-amino)-methyl]-aniline

(187) 4-[(N-aminocarbonylmethyl-N-methyl-amino)-methyl]-aniline

(188) 4-(azetidin-1-yl-methyl)-aniline

(189) 4-[(di-(2-methoxy-ethyl)-amino)-methyl]-aniline

(190) 4-[(N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl]-aniline

(191) [-(N-tert.butoxycarbonyl-3-amino-propyl)-N-methyl-aminomethyl]-aniline

(192) 4-[(N-(methylcabamoyl-methyl)-N-methyl-amino)-methyl]-aniline

(193) 4-[(N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl]-aniline

(194) 4-[(N-propyl-N-methyl-amino)-methyl]-aniline

(195) 4-[(N-(2-dimethylamino-ethyl)-N-methyl-amino)-methyl]-aniline

(196) 4-[(N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl]-aniline

(197) 4-[(N-(2-methoxy-ethyl)-N-methyl-amino)-methyl]-aniline

(198) 4-[(N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl]-aniline

(199) 4-[(N-(dioxolan-2-yl-methyl)-N-methyl-amino)-methyl]-aniline

(200) 4-(3-oxo-piperazin-1-yl-methyl)-aniline

(201) N-[di-(2-hydroxyethyl)-amino-methylcarbonyl]-N-methyl-p-phenylenediamine

(202) N-[(N-(2-methoxyethyl)-N-methyl-amino)-methylcarbonyl]-N-methyl-p-phenylenediamine

(203) N-[(N-(2-dimethylamino-ethyl)-N-methyl-amino)-methylcarbonyl]-N-methyl-p-phenylenediamine

(204) N-[(4-methyl-piperazin-1-yl)-methylcarbonyl]-N-methyl-p-phenylenediamine

(205) N-[(imidazol-1-yl)-methylcarbonyl]-N-methyl-p-phenylenediamine

(206) N-[(phthalimido-2-yl)-methylcarbonyl]-N-methyl-p-phenylenediamine

EXAMPLE XXI

4-(4-hydroxymethyl-piperidin-1-yl-methyl-amino)-aniline

1.1 g of 4-(4-ethoxycarbonyl-piperidin-1-yl-methyl-amino)-aniline are suspended in 15 ml of tetrahydrofuran. 175 mg of lithium borohydride are added at room temperature, stirred for 24 h, another 175 mg of lithium borohydride are added and after a further 7.5 hours 15 ml of water are added and the mixture is stirred for 10 minutes. It is extracted three times with 15 ml of ethyl acetate. The combined organic phases are washed with water and saturated saline solution, dried over sodium sulphate and concentrated by rotary evaporation. The residue is purified over a silica gel column with methylene chloride/methanol/ammonia 4:1:0.01 as eluant.

Yield: 200 mg (27% of theory) R_f value: 0.4 (silica gel, methylene chloride/methanol/ammonia 4:1:0.01)

Melting point: 157° C.

EXAMPLE XXII

methyl 4-methoxycarbonylmethyl-3-nitro-benzoate

54.3 g of methyl 3-nitro-benzoate and 29.0 g of methyl chloroacetate are dissolved in 100 ml of dimethylformamide and this solution is added dropwise at −10° C. to a solution of 78.5 g of potassium-tert. butoxide in 500 ml of dimethylformamide. The mixture is stirred for another 10 minutes

at room temperature and after this time the solution is poured onto 350 ml of concentrated hydrochloric acid in 2 l of ice water. The solution is stirred for 0.5 hours, the precipitate obtained is suction filtered and washed with water. The product is recrystallised from 150 ml of methanol and dried at 40° C. in vacuo.

Yield: 48.3 g of (51% of theory), contains about 20% of methyl 6-methoxycarbonylmethyl-3-nitro-benzoate. R_f value: 0.7 (silica gel, petroleum ether/ethyl acetate=1:1).

Melting point: 65–73° C.

The following compound is prepared analogously to Example XXII:

(1) ethyl 4-methoxycarbonylmethyl-3-nitro-benzoate

Prepared from ethyl 4-thoxycarbonylmethyl-3-nitro-benzoate

EXAMPLE XXIII

methyl 2-indolinone-6-carboxylate

48.3 g of methyl 4-methoxycarbonylmethyl-3-nitro-benzoate are dissolved in 800 ml of concentrated acetic acid, 5.0 g of palladium on carbon (10%) are added and the solution is hydrogenated for 2.5 hours at room temperature and 50 psi. The catalyst is filtered off and the filtrate is evaporated down. The residue is taken up in 150 ml of tert.-butylmethyl ether, filtered again and dried in vacuo at 100° C.

Yield: 28.6 g (98% of theory), R_f value: 0.4 (silica gel, methylene chloride/methanol=10:1).

Melting point: 208–211° C.

The following compound is prepared analogously to Example XXIII:

(1) ethyl 2-indolinone-6-carboxylate

Prepared from ethyl 4-methoxycarbonylmethyl-3-nitro-benzoate

EXAMPLE XXIV

1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone

15.0 g of ethyl 2-indolinone-6-carboxylate, 49.6 ml of triethyl orthobenzoate and 150 ml of acetic anhydride are stirred for 4 hours at 110° C. After this time the solvent is removed, the residue is recrystallised from petroleum ether and dried in vacuo at 50° C.

Yield: 16.9 g (61% of theory), R_f value: 0.5 (silica gel, petroleum ether/methylene chloride/ethyl acetate=5:4:1).

Melting point: 98–100° C. $C_{22}H_{21}NO_5$.

The following compounds are prepared analogously to Example XXIV:

(1) 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone

Prepared from methyl 2-indolinone-6-carboxylate, triethyl orthobenzoate and acetic anhydride

(2) 1-acetyl-3-(1-ethoxy-1-ethyl-methylene)-6-ethoxycarbonyl-2-indolinone

Prepared from ethyl 2-indolinone-6-carboxylate, triethyl orthopropionate and acetic anhydride

Preparation of the final compounds:

EXAMPLE 1

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

300 mg of resin obtained according to Example II are suspended in 3 ml of dimethylformamide and shaken with 0.2 g of 4-(piperidin-1-yl-methyl)-aniline for 22 hours at 70° C. Then it is filtered off and the resin is washed several times with methylene chloride, methanol and dimethylformamide. Then 1 ml of methanolic ammonia is added for 2 hours in order to eliminate the acetyl group. Then after further washing 4 ml of 10% trifluoroacetic acid in methylene chloride are added during another 60 minutes, the resin is separated off and the solution is evaporated down.

Yield: 69 mg. R_f value: 0.1 (silica gel, methylene chloride/methanol=9:1) $C_{28}H_{28}N_4O_2$.

Mass spectrum: m/z=452 (m^+).

The following compounds are prepared analogously to Example 1:

(1) 3-Z-(1-Anilino-1-phenyl-methylene)-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and aniline $C_{22}H_{17}N_3O_2$.

Mass spectrum: m/z=355 (m^+).

(2) 3-Z-[1-(4-dimethylaminomethyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-dimethylaminomethyl-aniline $C_{25}H_{24}N_4O_2$

Mass spectrum: m/z=412 (m^+).

(3) 3-Z-[1-(4-(2-dimethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(2-diethylamino-ethyl)-aniline $C_{28}H_{30}N_4O_2$

Mass spectrum: m/z=454 (m^+).

(4) 3-Z-[1-(4-(morpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(morpholin-4-yl-methyl)-aniline R_f value: 0.50 (silica gel, methylene chloride/methanol=4:1) $C_{27}H_{26}N_4O_3$

Mass spectrum: m/z=454 (m^+).

(5) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(1-oxo-thiomorpholin-4-yl-methyl)-aniline R_f value: 0.30 (silica gel, methylene chloride/methanol=9:1) $C_{27}H_{26}N_4O_3S$

Mass spectrum: m/z=486 (m^+)

(6) 3-Z-[1-(4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-aniline R_f value: 0.30 (silica gel, methylene chloride/methanol=9:1) $C_{27}H_{26}N_4O_4S$

Mass spectrum: m/z=502 (m^+).

(7) 3-Z-[1-(4-(benzylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-[N-(phenyl-methyl)-N-tert.butoxycarbonyl-aminomethyl]-aniline R_f value: 0.40 (silica gel, methylene chloride/methanol=4:1) $C_{30}H_{26}N_4O_2$

Mass spectrum: m/z=474 (m^+).

(8) 3-Z-[1-(4-(amino-methyl)-anilino)-1-phenyl-methylene-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(N-tert.butoxycarbonyl-aminomethyl)-aniline R_f value: 0.10 (silica gel, methylene chloride/methanol=4:1) $C_{23}H_{20}N_4O_2$

Mass spectrum: m/z=384 (m^+).

(9) 3-Z-[1-(4-(2,6-dimethylpiperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(2,6-dimethylpiperidin-1-yl-methyl)-aniline R_f value: 0.45 (silica gel, methylene chloride/methanol=4:1) $C_{30}H_{32}N_4O_2$

Mass spectrum: m/z=480 (m^+).

(10) 3-Z-[1-(4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(pyrrolidin-1-yl-methyl)-aniline R_f value: 0.15 (silica gel, methylene chloride/methanol=4:1) $C_{27}H_{26}N_4O_2$

Mass spectrum: m/z=438 (m^+).

(11) 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 3-dimethylaminomethyl-aniline R_f value: 0.23 (silica gel, methylene chloride/methanol=4:1) $C_{25}H_{24}N_4O_2$

Mass spectrum: m/z=412 (m^+).

(12) 3-Z-[1-(3-(N-methyl-N-ethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 3-(N-methyl-N-ethyl-aminomethyl)-aniline R_f value: 0.23 (silica gel, methylene chloride/methanol=4:1). $C_{26}H_{26}N_4O_2$

Mass spectrum: m/z=426 (m^+).

(13) 3-Z-[1-(3-(methylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(N-tert.butoxycarbonyl-N-methyl-aminomethyl)-aniline R_f value: 0.06 (silica gel, methylene chloride/methanol=4:1) $C_{24}H_{22}N_4O_2$

Mass spectrum: m/z=399 ($m+H^+$).

(14) 3-Z-[1-(3-hydroxymethyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 3-amino-benzyl alcohol R_f value: 0.7 (silica gel, methylene chloride/methanol=4:1) $C_{23}H_{19}N_3O_3$

Mass spectrum: m/z=385 (m^+).

(15) 3-Z-[1-(4-methoxycarbonylmethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-(N-methoxycarbonylmethyl-N-tert.butoxycarbonyl-aminomethyl)-aniline R_f value: 0.40 (silica gel, methylene chloride/methanol=9:1) $C_{26}H_{24}N_4O_4$

Mass spectrum: m/z=457 ($m+H^+$).

(16) 3-Z-[1-(4-(N-methylsulphonyl-N-(dimethylaminocarbonyl-methyl)-amino)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-(N-methylsulphonyl-N-(dimethylaminocarbonylmethyl)-amino)-aniline R_f value: 0.40 (silica gel, methylene chloride/methanol=9:1) $C_{27}H_{27}N_5O_5S$

Mass spectrum: m/z=533 (m^+).

(17) 3-Z-[1-(4-(N-acetyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-(N-acetyl-aminomethyl)-aniline R_f value: 0.70 (silica gel, methylene chloride/methanol=4:1) $C_{25}H_{22}N_4O_3$

Mass spectrum: m/z=426 (m^+).

(18) 3-Z-[1-(3,4-dimethoxy-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 3,4-dimethoxy-aniline R_f value: 0.40 (silica gel, methylene chloride/methanol=9:1) $C_{24}H_{21}N_3O_4$

Mass spectrum: m/z=415 (m^+).

(19) 3-Z-[1-(4-(morpholin-4-yl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-morpholin-4-yl-aniline R_f value: 0.20 (silica gel, methylene chloride/methanol=9:1) $C_{26}H_{24}N_4O_3$

Mass spectrum: m/z=440 (m^+).

(20) 3-Z-[1-(4-acetylamino-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-acetylamino-aniline R_f value: 0.25 (silica gel, methylene chloride/methanol=9;1) $C_{24}H_{20}N_4O_3$

Mass spectrum: m/z=412 (m^+).

(21) 3-Z-[1-(4-amino-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-amino-aniline R_f value: 0.40 (silica gel, methylene chloride/methanol=9:1) $C_{22}H_{18}N_4O_2$

Mass spectrum: m/z=370 (m^+).

(22) 3-Z-[1-(4-N-methyl-N-acetyl-amino-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-(N-methyl-N-acetyl-amino)-aniline $C_{25}H_{22}N_4O_3$

Mass spectrum: m/z=426 (m^+).

(23) 3-Z-[1-(4-ethoxycarbonyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and ethyl 4amino-benzoate $C_{25}H_{21}N_3O_4$

Mass spectrum: m/z=427 (m^+).

(24) 3-Z-[1-(4-carboxy-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-amino-benzoic acid R_f value: 0.11 (silica gel, methylene chloride/methanol=9:1) $C_{23}H_{17}N_3O_4$

Mass spectrum: m/z=398 ($m-H^+$).

(25) 3-Z-[1-(4-benzylcarbamoyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and 4-amino-benzoic acid-benzylamide R_f value: 0.21 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{24}N_4O_3$

Mass spectrum: m/z=488 (m^+).

(26) 3-Z-[1-(cyclohexyl-amino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II and cyclohexylamine R_f value: 0.60 (silica gel, methylene chloride/methanol=9:1) $C_{22}H_{23}N_3O_2$

Mass spectrum: m/z=361 (m^+).

(27) 3-Z-[1-(4-amino-cyclohexyl-amino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-amino-cyclohexylamine $C_{22}H_{24}N_4O_2$

Mass spectrum: m/z=376 (m^+).

(28) 3-Z-[1-(N-methyl-piperidine-4-yl-amino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 4-amino-1-methyl-piperidine R_f value: 0.15 (silica gel, methylene chloride/methanol=4:1) $C_{22}H_{24}N_4O_2$

Mass spectrum: m/z=376 (m^+).

(29) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(2) and 4-(piperidin-1-yl-methyl)-aniline R_f value: 0.30 (silica gel, methylene chloride/methanol=4:1) $C_{23}H_{26}N_4O_2$

Mass spectrum: m/z=390 (m^+).

(30) 3-Z-f 1-(3-dimethylaminomethyl-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(2) and 3-dimethylaminomethyl-aniline R_f value: 0.51 (silica gel, methylene chloride/methanol=4:1) $C_{20}H_{22}N_4O_2$

Mass spectrum: m/z=351 ($m+H^+$).

(31) 3-Z-[1-(4-(N-methyl-N-benzyl-aminomethyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(2) and 4-(N-methyl-N-benzyl-aminomethyl)-aniline R_f value: 0.73 (silica gel, methylene chloride/methanol=4:1) $C_{26}H_{26}N_4O_2$

Mass spectrum: m/z=426 (m^+).

(32) 3-Z-[1-(4-(N-methylsulphonyl-N-(2-dimethylamino-ethyl)-amino)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(2) and 4-(N-methylsulphonyl-N-(2-dimethylamino-ethyl)-amino)-aniline $C_{22}H_{27}N_5O_4S$

Mass spectrum: m/z=458 ($m+H^+$).

(33) 3-Z-[1-(4-chloro-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and 4-chloro-aniline R_f value: 0.10 (silica gel, methylene chloride/methanol=9:1) $C_{17}H_{14}ClN_3O_2$

Mass spectrum: m/z=327/329 (m^+).

(34) 3-Z-[1-(3-chloro-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and 3-chloro-aniline R_f value: 0.11 (silica gel, methylene chloride/methanol=9:1) $C_{17}H_{14}ClN_3O_2$

Mass spectrum: m/z=327/329 (m^+).

(35) 3-Z-[1-(4-methoxycarbonyl-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and methyl 4-amino-benzoate R_f value: 0.11 (silica gel, methylene chloride/methanol=9:1) $C_{19}H_{17}N_3O_4$

Mass spectrum: m/z=351 (m^+).

(36) 3-Z-[1-(4-carboxy-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and 4-amino-benzoic acid $C_{18}H_{15}N_3O_4$

Mass spectrum: m/z=336 ($m-H^+$).

(37) 3-Z-[1-(4-methyl-3-nitro-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(2) and 4-methyl-3-nitro-aniline R_f value: 0.82 (silica gel, methylene chloride/methanol=4:1) $C_{18}H_{16}N_4O_4$

Mass spectrum: m/z=352 (m^+).

(38) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(4) and 4-(piperidin-1-yl-methyl)-aniline R_f value: 0.37 (silica gel, methylene chloride/methanol=4:1) $C_{25}H_{30}N_4O_2$

Mass spectrum: m/z=418 (m^+).

(39) 3-Z-[1-(3-dimethylaminomethyl-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(4) and 3-dimethylaminomethyl-aniline R_f value: 0.42 (silica gel, methylene chloride/methanol=4:1) $C_{22}H_{26}N_4O_2$

Mass spectrum: m/z=378 (m^+).

(40) 3-Z-[1-(4-(N-methyl-N-benzyl-aminomethyl)-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(4) and 4-(N-methyl-N-benzyl-aminomethyl)-aniline R_f value: 0.81 (silica gel, methylene chloride/methanol=4:1) $C_{28}H_{30}N_4O_2$

Mass spectrum: m/z=454 (m^+).

(41) 3-Z-[1-(4-(N-methylsulphonyl-N-(2-dimethylamino-ethyl)-amino)-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II(4) and 4-(N-methylsulphonyl-N-(2-dimethylamino-ethyl)-amino)-aniline R_f value: 0.59 (silica gel, methylene chloride/methanol=4:1) $C_{24}H_{31}N_5O_4S$

Mass spectrum: m/z=486 ($m+H^+$).

(42) 3-Z-[1-(4-chloro-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and 4-chloro-aniline R_f value: 0.17 (silica gel, methylene chloride/methanol=9:1) $C_{19}H_{18}ClN_3O_2$

Mass spectrum: m/z=355/357 (m^+).

(43) 3-Z-[1-(3-chloro-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and 3-chloro-aniline R_f value: 0.12 (silica gel, methylene chloride/methanol=9:1).

$C_{19}H_{18}ClN_3O_2$

Mass spectrum: m/z=355/357 (m^+).

(44) 3-Z-[1-(4-methoxycarbonyl-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and methyl 4-amino-benzoate R_f value: 0.8 (silica gel, methylene chloride/methanol=4:1) $C_{21}H_{21}N_3O_4$

Mass spectrum: m/z=379 (m^+).

(45) 3-Z-[1-(4-carboxy-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and 4-amino-benzoic acid $C_{20}H_{19}N_3O_4$

Mass spectrum: m/z=364 ($m-H^+$).

(46) 3-Z-[1-(4-methyl-3-nitro-anilino)-1-propyl-methylene]-6-carbamoyl-2-indolinone

Prepared from the resin obtained according to Example II(4) and 4-methyl-3-nitro-aniline R_f value: 0.86 (silica gel, methylene chloride/methanol=4:1) $C_{20}H_{20}N_4O_4$

Mass spectrum: m/z=380 (m^+).

EXAMPLE 2

3-Z-[1-(3-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

2.0 g of resin obtained according to Example II are reacted analogously to Example 1 with 2.0 g of

3-aminobenzyl alcohol in 20 ml of dimethylformamide for 22 hours at 70° C. Then the solvent is suction filtered and the resin is washed several times with dimethylformamide and methylene chloride. Then 200 mg of the moist charged resin are suspended in 2 ml of methylene chloride and left to stand with 0.2 ml of methanesulphonic acid chloride and 0.1 ml of triethylamine for 2 hours at room temperature. Then the resin is washed several times with methylene chloride, suspended in 2 ml of methylene chloride and combined with 0.2 ml of piperidine. After 1 hour the resin is washed with methylene chloride and dimethylformamide and then treated with trifluoroacetic acid analogously to Example 1.

Yield: 15 mg. R_f value: 0.30 (silica gel, methylene chloride/methanol=4:1) $C_{28}H_{28}N_4O_2$

Mass spectrum: m/z=452 (m^+).

The following compounds are prepared analogously to Example 2:

(1) 3-Z-[1-(3-diethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and diethylamine R_f value: 0.80 (silica gel, methylene chloride/methanol 4:1) $C_{27}H_{28}N_4O_2$

Mass spectrum: m/z=440 (m^+).

(2) 3-Z-[1-(3-(benzylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and benzylamine R_f value: 0.80 (silica gel, methylene chloride/methanol=4:1) $C_{30}H_{26}N_4O_2$

Mass spectrum: m/z=474 (m^+).

(3) 3-Z-[1-(3-(N-methyl-N-benzyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and N-methyl-benzylamine R_f value: 0.80 (silica gel, methylene chloride/methanol=4:1) $C_{31}H_{28}N_4O_2$

Mass spectrum: m/z=488 (m^+).

(4) 3-Z-[1-(3-(butylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and butylamine R_f value: 0.40 (silica gel, methylene chloride/methanol=4:1) $C_{27}H_{28}N_4O_2$

Mass spectrum: m/z=440 (m^+).

(5) 3-Z-[1-(3-(aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and ammonia $C_{23}H_{20}N_4O_2$

Mass spectrum: m/z=385 ($m+H^+$).

(6) 3-Z-[1-(3-(N-(3-dimethylaminopropyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 1-dimethylamino-3-methylaminopropane R_f value: 0.67 (silica gel, methylene chloride/methanol=4:1) $C_{29}H_{33}N_5O_2$

Mass spectrum: m/z=484 ($m+H^+$).

(7) 3-Z-[1-(3N-(2-dimethylaminoethyl)-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone-trifluoroacetate

Prepared from the resin obtained according to Example II and 1-dimethylamino-2-methylaminoethane R_f value: 0.40 (silica gel, methylene chloride/methanol=4:1) $C_{28}H_{31}N_5O_2$

Mass spectrum: m/z=470 ($m+H^+$).

EXAMPLE 3

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

1.5 g of 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 1.1 g of 4-(piperidin-1-yl-methyl)-aniline are dissolved in 15 ml of dimethylformamide and stirred for 45 minutes at 100° C. After cooling 5.0 ml of piperidine are added and the mixture is stirred for another 3 hours at room temperature. The solvent is removed and the residue purified over an aluminium oxide column (activity: 2–3) with methylene chloride/ethanol (100:3) as eluant.

Yield: 1.1 g (58% of theory), R_f value: 0.5 (aluminium oxide, methylene chloride/ethanol=100:3) $C_{30}H_{31}N_3O_3$

Mass spectrum: m/z=481 [M^+].

The following compounds are prepared analogously to Example 3:

(1) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-bromoaniline R_f value: 0.4 (silica gel, toluene/ethyl acetate=5:1) $C_{24}H_{19}BrN_2O_3$

Mass spectrum: m/z=462/464 [M^+].

(2) 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 3-(dimethylaminomethyl)-aniline R_f value: 0.5 (aluminium oxide, methylene chloride/ethanol=30:1) $C_{27}H_{27}N_3O_3$

ESI mass spectrum: m/z=442 [$M+H^+$].

(3) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(dimethylaminomethyl)-aniline R_f value: 0.7 (aluminium oxide, ethyl acetate/ethanol=20:1) $C_{27}H_{27}N_3O_3$

ESI mass spectrum: m/z=442 [$M+H^+$].

(4) 3-Z-[1-(4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-aniline R_f value: 0.6 (silica gel, methylene chloride/ethanol=5:1) $C_{32}H_{35}N_3O_3$

Mass spectrum: m/z=509 [M^+].

(5) 3-Z-[1-(4-(2-dimethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(2-dimethylamino-ethyl)-aniline R_f value: 0.2 (silica gel, methylene chloride/ethanol=5:1) $C_{28}H_{29}N_3O_3$

Mass spectrum: m/z=455 [M^+].

(6) 3-Z-[1-(4-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-aniline R_f value: 0.4 (aluminium oxide, methylene chloride/ethanol=20:1) $C_{30}H_{32}N_4O_4$

Mass spectrum: m/z=512 [M^+].

(7) 3-Z-[1-(4-tert.butyloxycarbonyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-tert.butyloxycarbonyl-aniline R_f value: 0.4 (aluminium oxide, methylene chloride/ethanol=40:1) $C_{29}H_{28}N_2O_5$

Mass spectrum: m/z=484 [M^+].

(8) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-aniline R_f value: 0.2 (aluminium oxide, methylene chloride/ethanol=40:1) $C_{31}H_{34}N_4O_4$

Mass spectrum: m/z=526 [M^+].

(9) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylenediamine R_f value: 0.3 (aluminium oxide, methylene chloride/ethanol=40:1) $C_{29}H_{32}N_4O_5S$

Mass spectrum: m/z=548 [M^+].

(10) 3-Z-[1-(4-(4-methyl-piperazin-1-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(4-methyl-piperazin-1-yl)-aniline R_f value: 0.3 (aluminium oxide, ethyl acetate) $C_{29}H_{30}N_4O_3$

ESI mass spectrum: m/z=483 [$M+H^+$].

(11) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-methyl-amino)-aniline R_f value: 0.5 (aluminium oxide, methylene chloride/ethanol=20:1) $C_{29}H_{32}N_4O_3$

ESI mass spectrum: m/z=485 [$M+H^+$].

(12) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-(3-dimethylamino-propyl)-N-methyl-amino)-aniline R_f value: 0.5 (aluminium oxide, ethyl acetate) $C_{30}H_{34}N_4O_3$

ESI mass spectrum: m/z=499 [$M+H^+$].

(13) 3-Z-[1-(4-(N-methyl-acetylamino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-amino-N-methyl-acetanilide R_f value: 0.3 (silica gel, methylene chloride/ethanol=15:1) $C_{27}H_{25}N_3O_4$

Mass spectrum: m/z=455 [M^+].

(14) 3-Z-[1-(4-(N-methyl-methylsulphonylamino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and N-(4-aminophenyl)-N-methyl-methanesulphonamide R_f value: 0.8 (aluminium oxide, ethyl acetate) $C_{26}H_{25}N_3O_5S$

Mass spectrum: m/z=491 [M^+].

(15) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and N-(3-dimethylamino-propyl)-N-methylsulphonyl-p-phenylenediamine R_f value: 0.6 (silica gel, methylene chloride/ethanol/ammonia=5:2:0.01) $C_{30}H_{34}N_4O_5S$

ESI mass spectrum: m/z=563 [$M+H^+$].

(16) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl)-amino)-aniline R_f value: 0.6 (silica gel, methylene chloride/ethanol=10:1) $C_{29}H_{30}N_4O_6S$

ESI mass spectrum: m/z=561 [$M-H^-$].

(17) 3-Z-[1-(4-(imidazol-4-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(imidazol-4-yl)-aniline R_f value: 0.5 (silica gel, methylene chloride/ethanol/ammonia=10:1:0.01) $C_{27}H_{22}N_4O_3$

Mass spectrum: m/z=450 [M^+].

(18) 3-Z-[1-(4-(tetrazol-5-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(tetrazol-5-yl)-aniline R_f value: 0.5 (silica gel, methylene chloride/ethanol=5:1) $C_{25}H_{20}N_6O_3$

ESI mass spectrum: m/z=451 [$M-H^-$].

(19) 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-benzyl-N-methyl-aminomethyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/ethanol=10:1) $C_{33}H_{31}N_3O_3$

ESI mass spectrum: m/z=516 [$M-H^-$].

(20) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-propionyl-amino)-aniline)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-[N-(2-dimethylamino-ethyl)-N-propionyl-amino]-aniline R_f value: 0.2 (silica gel, methylene chloride/ethanol=5:1) $C_{31}H_{34}N_4O_4$

ESI mass spectrum: m/z=525 [$M-H^-$].

(21) 3-Z-[1-(4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(pyrrolidin-1-yl-methyl)-aniline R_f value: 0.1 (silica gel, methylene chloride/ethanol=5:1) $C_{29}H_{29}N_3O_3$

ESI mass spectrum: m/z=466 [$M-H^-$].

(22) 3-Z-[1-(4-(N-methyl-N-phenethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and (N-phenethyl-N-methyl-aminomethyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/ethanol=10:1) $C_{34}H_{33}N_3O_3$

ESI mass spectrum: m/z=530 [$M-H^-$].

(23) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and

N-dimethylaminomethylcarbonyl-N-methyl-p-phenylenediamine R_f value: 0.1 (silica gel, methylene chloride/ethanol=10:1) $C_{29}H_{30}N_4O_4$

ESI mass spectrum: m/z=497 [M−H⁻].

(24) 3-Z-[1-(4-(N-2-dimethylamino-ethyl)-N-ethylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-ethylsulphonyl-p-phenylenediamine R_f value: 0.6 (silica gel, methylene chloride/ethanol=5:1) $C_{30}H_{34}N_4O_5S$

ESI mass spectrum: m/z=561 [M−H⁻].

(25) 3-Z-[1-(4-(N-tert.butoxycarbonyl-N-ethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and 4-(N-tert.butoxycarbonyl-N-ethyl-aminomethyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{32}H_{35}N_3O_5$

ESI mass spectrum: m/z=540 [M−H⁻].

(26) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-ethyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-ethyl-methylene)-6-ethoxycarbonyl-2-indolinone and 4-(piperidin-1-yl-methyl)-aniline R_f value: 0.9 (silica gel, methylene chloride/ethanol=5:1) $C_{26}H_{31}N_3O_3$

ESI mass spectrum: m/z=432 [M−H⁻].

(27) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-ethyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-ethyl-methylene)-6-ethoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylenediamine R_f value: 0.3 (silica gel, methylene chloride/ethanol=5:1) $C_{25}H_{32}N_4O_5S$

ESI mass spectrum: m/z=499 [M−H⁻].

(28) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(dimethylaminomethyl)-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol=5:1) $C_{26}H_{25}N_3O_3$

ESI mass spectrum: m/z=428 [M+H⁺].

(29) 3-Z-[1-(4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-aniline R_f value: 0.5 (RP 8, methanol/five percent saline solution=4:1) $C_{31}H_{33}N_3O_3$

ESI mass spectrum: m/z=496 [M+H⁺].

(30) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-methylsulphonyl-p-phenylenediamine R_f value: 0.6 (silica gel, methylene chloride/methanol=5:1) $C_{28}H_{30}N_4O_5S$

ESI mass spectrum: m/z=533 [M−H⁻].

(31) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(3-dimethylamino-propyl)-N-methylsulphonyl-p-phenylenediamine R_f value: 0.5 (aluminium oxide, methylene chloride/methanol=30:1) $C_{29}H_{32}N_4O_5S$

ESI mass spectrum: m/z=547 [M−H⁻].

(32) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-dimethylaminocarbonyl-methyl-N-methylsulphonyl)-amino)-aniline R_f value: 0.5 (aluminium oxide, methylene chloride/methanol=20:1) $C_{28}H_{28}N_4O_6S$

ESI mass spectrum: m/z=547 [M−H⁻].

(33) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-acetyl-N-dimethylaminocarbonylmethyl)-amino)-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol=10:1) $C_{29}H_{28}N_4O_5$

ESI mass spectrum: m/z=511 [M−H⁻].

(34) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-dimethylaminocarbonyl-methyl)-amino)-aniline R_f value: 0.6 (aluminium oxide, methylene chloride/methanol=30:1) $C_{27}H_{26}N_4O_4$

ESI mass spectrum: m/z=469 [M−H⁻].

(35) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(3-dimethylamino-propyl)-N-acetyl-p-phenylenediamine R_f value: 0.5 (aluminium oxide, methylene chloride/methanol=20:1) $C_{30}H_{32}N_4O_4$

ESI mass spectrum: m/z=511 [M−H⁻].

(36) 3-Z-[1-(4-(N-methylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-methylaminocarbonylmethyl-N-methylsulphonyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{27}H_{26}N_4O_6S$

ESI mass spectrum: m/z=533 [M−H⁻].

(37) 3-Z-[1-(4-((imidazolidin-2,4-dion-5-ylidene)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((imidazolidin-2,4-dion-5-ylidene)-methyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol=10:1) $C_{27}H_{20}N_4O_5$

ESI mass spectrum: m/z=479 [M−H⁻].

(38) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((2-

dimethylamino-ethyl)-carbonyl)-N-methyl-p-phenylenediamine R_f value: 0.5 (aluminium oxide, methylene chloride/methanol=20:1) $C_{29}H_{30}N_4O_4$

ESI mass spectrum: m/z=497 [M−H⁻].

(39) 3-Z-[1-(4-(N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-tert.butoxycarbonyl-aminomethyl)-aniline R_f value: 0.3 (aluminium oxide, methylene chloride/methanol=20:1) $C_{29}H_{29}N_3O_5$

ESI mass spectrum: m/z=498 [M−H⁻].

(40) 3-Z-[1-(4-(2-oxo-pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(2-oxo-pyrrolidin-1-yl-methyl)-aniline R_f value: 0.3 (silica gel, methylene chloride/methanol=20:1) $C_{28}H_{25}N_3O_4$

ESI mass spectrum: m/z=466 [M−H⁻].

(41) 3-Z-[1-(4-(N-aminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-aminocarbonylmethyl-N-methylsulphonyl-p-phenylenediamine R_f value: 0.7 (silica gel, methylene chloride/methanol=5:1) $C_{26}H_{24}N_4O_6S$

ESI mass spectrum: m/z=519 [M−H⁻].

(42) 3-Z-[1-(4-(thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(thiomorpholin-4-yl-methyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol=15:1) $C_{28}H_{27}N_3O_3S$

ESI mass spectrum: m/z=484 [M−H⁻].

(43) 3-Z-[1-(4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{28}H_{27}N_3O_5S$

ESI mass spectrum: m/z=516 [M−H⁻].

(44) 3-Z-[1-(4-(N-cyanomethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-cyanomethyl-N-methyl-sulphonyl-p-phenylenediamine R_f value: 0.6 (silica gel, methylene chloride/methanol=10:1) $C_{26}H_{22}N_4O_5S$

ESI mass spectrum: m/z=501 [M−H⁻].

(45) 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-ethyl-N-tert.butoxycarbonyl-aminomethyl)-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol=10:1) $C_{31}H_{33}N_3O_5$

ESI mass spectrum: m/z=526 [M−H⁻].

(46) 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-benzyl-N-methyl-aminomethyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{32}H_{29}N_3O_3$

ESI mass spectrum: m/z=502 [M−H⁻].

(47) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1-oxo-thiomorpholin-4-yl-methyl)-aniline R_f value: 0.7 (silica gel, methylene chloride/methanol=10:1) $C_{28}H_{27}N_3O_4S$

ESI mass spectrum: m/z=500 [M−H⁻].

(48) 3-Z-[1-(4-(2-(imidazol-4-yl)-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(2-(imidazol-4-yl)-ethyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol=5:1) $C_{28}H_{24}N_4O_3$

ESI mass spectrum: m/z=463 [M−H⁻].

(49) 3-Z-[1-(4-(morpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(morpholin-4-yl-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{28}H_{27}N_3O_4$

ESI mass spectrum: m/z=468 [M−H⁻].

(50) 3-Z-[1-(4-((4-methyl-piperazin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((4-methyl-piperazin-1-yl)-methyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol 5:1) $C_{29}H_{30}N_4O_3$

ESI mass spectrum: m/z=481 [M−H⁻].

(51) 3-Z-[1-(4-((2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino)-aniline R_f value: 0.7 (silica gel, methylene chloride/methanol=10:1) $C_{34}H_{34}N_4O_5S$

ESI mass spectrum: m/z=609 [M−H⁻].

(52) 3-Z-[1-(4-cyclohexylamino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-cyclohexyl-p-phenylenediamine R_f value: 0.8 (silica gel, methylene chloride/methanol=10:1) $C_{29}H_{28}N_2O_3$

ESI mass spectrum: m/z=451 [M−H⁻].

(53) 3-Z-[1-(4-(pyridin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(pyridin-4-yl-methyl)-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01) $C_{29}H_{23}N_3O_3$

ESI mass spectrum: m/z=460 [M−H⁻].

(54) 3-Z-[1-(4-(imidazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(imidazol-1-yl-methyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol/ammonia=10:1:0.01) $C_{27}H_{22}N_4O_3$

ESI mass spectrum: m/z=449 [M−H⁻].

(55) 3-Z-[1-(4-(imidazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(imidazol-1-yl-methyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol/ammonia=10:1:0.01) $C_{27}H_{22}N_4O_3$

ESI mass spectrum: m/z=449 [M−H⁻].

(56) 3-Z-[1-(N-methyl-piperidine-4-yl-amino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-amino-1-methyl-piperidine R_f value: 0.3 (silica gel, methylene chloride/methanol=5:1) $C_{23}H_{25}N_3O_3$

ESI mass spectrum: m/z=390 [M−H⁻].

(57) 3-Z-[1-(4-(imidazol-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(imidazol-4-yl-methyl)-aniline R_f value: 0.2 (silica gel, methylene chloride/methanol=5:1) $C_{27}H_{22}N_4O_3$

ESI mass spectrum: m/z=449 [M−H⁻].

(58) 3-Z-[1-(4-((4-hydroxy-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((4-hydroxy-piperidin-1-yl)-methyl)-aniline R_f value: 0.1 (silica gel, methylene chloride/methanol=10:1) $C_{29}H_{29}N_3O_3$

ESI mass spectrum: m/z=482 [M−H⁻].

(59) 3-Z-[1-(4-((4-methoxy-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((4-methoxy-piperidin-1-yl)-methyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol=10:1) $C_{30}H_{31}N_3O_4$

ESI mass spectrum: m/z=496 [M−H⁻].

(60) 3-Z-[1-(4-benzyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-benzyl-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol=10:1) $C_{30}H_{24}N_2O_3$

Melting point: 224° C.

(61) 3-Z-[1-(4-(N-(3-trifluoroacetylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(3-trifluoroacetylamino-propyl)-N-methylsulphonyl-p-phenylenediamine R_f value: 0.5 (aluminium oxide, methylene chloride/methanol=20:1) $C_{29}H_{27}F_3N_4O_6S$

ESI mass spectrum: m/z=615 [M−H⁻].

(62) 3-Z-[1-(4-tert.butoxycarbonylmethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-ethoxycarbonyl-2-indolinone and tert.butyl 4-aminophenylacetate R_f value: 0.5 (aluminium oxide, ethyl acetate) $C_{30}H_{30}N_2O_5$

ESI mass spectrum: m/z=497 [M−H⁻].

(63) 3-Z-[1-(4-tert.butoxycarbonyl-anilino)-1-ethyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-ethylmethylen)-6-ethoxycarbonyl-2-indolinone and 4-tert.butoxycarbonyl-aniline R_f value: 0.4 (aluminium oxide, methylene chloride/ethanol=20:1) $C_{25}H_{28}N_2O_5$

ESI mass spectrum: m/z=435 [M−H⁻].

(64) 3-Z-[1-(4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{33}H_{36}N_4O_5$

ESI mass spectrum: m/z=567 [M−H⁻].

(65) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1-methyl-imidazol-2-yl)-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol=5:1) $C_{27}H_{22}N_4O_3$

ESI mass spectrum: m/z=449 [M−H⁻].

(66) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-nitro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 6-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-amino-nitrobenzene R_f value: 0.6 (silica gel, methylene chloride/methanol=5:1) $C_{28}H_{29}N_5O_7S$.

ESI mass spectrum: m/z=578 [M−H⁻].

(67) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-amino-aniline R_f value: 0.5 (aluminium oxide, methylene chloride/methanol=20:1) $C_{28}H_{31}N_5O_5S$

ESI mass spectrum: m/z=548 [M−H⁻]. (68) 3-Z-[1-(4-((3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino)-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol=10:1) $C_{35}H_{36}N_4O_5S$

ESI mass spectrum: m/z=623 [M−H⁻].

(69) 3-Z-[1-(4N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-chloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-chloro-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{28}H_{29}ClN_4O_5S$

ESI mass spectrum: m/z=567/569 [M−H⁻].

(70) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-dimethylaminomethylcarbonyl-N-methyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{28}H_{28}N_4O_4$

ESI mass spectrum: m/z=483 [M−H⁻].

(71) 3-Z-[1-(4N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{29}H_{30}N_4O_4$

ESI mass spectrum: m/z=497 [M−H⁻].

(72) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-propionyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-propionyl-amino)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{32}N_4O_4$

ESI mass spectrum: m/z=511 [M−H⁻].

(73) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-butyryl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-butyryl-amino)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{31}H_{34}N_4O_4$

ESI mass spectrum: m/z=525 [M−H⁻].

(74) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-isobutyryl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-isobutyryl-amino)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{31}H_{34}N_4O_4$

ESI mass spectrum: m/z=525 [M−H⁻].

(75) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-benzoyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-benzoyl-amino)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{34}H_{32}N_4O_4$

ESI mass spectrum: m/z=559 [M−H⁻].

(76) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-amino-aniline R_f value: 0.5 (aluminium oxide, methylene chloride/methanol=20:1) $C_{29}H_{31}N_5O_4$

ESI mass spectrum: m/z=512 [M−H⁻].

(77) 3-Z-[1-(4-(4-hydroxymethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene-6-methoxycarbonyl-2-indolinone and 4-(4-hydroxymethyl-piperidin-1-yl-methyl-amino)-aniline R_f value: 0.3 (silica gel, methylene chloride/methanol=5:1) $C_{30}H_{31}N_3O_4$

ESI mass spectrum: m/z=496 [M−H⁻].

(78) 3-Z-[1-(4-(2-(4-hydroxy-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(2-(4-hydroxy-piperidin-1-yl)-ethyl-amino)-aniline R_f value: 0.3 (silica gel, methylene chloride/methanol=5:1) $C_{30}H_{31}N_3O_4$

ESI mass spectrum: m/z=496 [M−H⁻].

(79) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-propylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-propylsulphonyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{34}N_4O_5S$

ESI mass spectrum: m/z=561 [M−H⁻].

(80) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-butylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-butylsulphonyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{31}H_{36}N_4O_5S$

ESI mass spectrum: m/z=575 [M−H⁻].

(81) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-amino)-anilino)-1-phenyl-9-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{33}H_{32}N_4O_5S$

ESI mass spectrum: m/z=595 [M−H⁻].

(82) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{34}H_{34}N_4O_5S$

ESI mass spectrum: m/z=609 [M−H⁻].

(83) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-ethylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-ethylsulphonyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{29}H_{32}N_4O_5S$

ESI mass spectrum: m/z=547 [M−H⁻].

(84) 3-Z-[1-(4-((imidazolidin-2,4-dion-5-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((imidazolidin-2,4-dion-5-yl)-methyl)-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol=5:1) $C_{27}H_{22}N_4O_5$

ESI mass spectrum: m/z=481 [M−H⁻].

(85) 3-Z-[1-(4-((3-hydroxy-pyrrolidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((3-hydroxy-

pyrrolidin-1-yl)-methyl)-aniline R_f value: 0.1 (silica gel, methylene chloride/methanol=10:1) $C_{28}H_{27}N_3O_4$

ESI mass spectrum: m/z=468 [M−H⁻].

(86) 3-Z-[1-(4-(cyclohexylyl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(cyclohexyl-methyl)-aniline (Eur. J. Med. Chem. Chim. Ther. 1992, 27, 537-544) R_f value: 0.6 (silica gel, methylene chloride/methanol=10:1) $C_{30}H_{30}N_2O_3$

ESI mass spectrum: m/z=465 [M−H⁻].

(87) 3-Z-[1-(4-(cyclohexyl-carbonyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4cyclohexyl-carbonyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{30}H_{28}N_2O_4$

ESI mass spectrum: m/z=479 [M−H⁻].

(88) 3-Z-[1-(4-diethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(diethylamino-methyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol=10:1) $C_{28}H_{29}N_3O_3$

ESI mass spectrum: m/z 454 [M−H⁻].

(89) 3-Z-[1-(4-(N-(n-hexyl)-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(n-hexyl)-N-methyl-aminomethyl)-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol=10:1) $C_{31}H_{35}N_3O_3$

ESI mass spectrum: m/z=496 [M−H⁻].

(90) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{32}H_{30}N_4O_5$

ESI mass spectrum: m/z=549 [M−H⁻].

(91) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{35}H_{34}N_4O_5$

ESI mass spectrum: m/z=589 [M−H⁻].

(92) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(pyridine-3-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-(pyridine-3-carbonyl)-amino)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{33}H_{31}N_5O_4$

ESI mass spectrum: m/z 560 [M−H⁻].

(93) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-(phenyl-acetyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-(phenyl-acetyl)-amino)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{35}H_{34}N_4O_4$

ESI mass spectrum: m/z=573 [M−H⁻].

(94) 3-Z-[1-(4-(N-ethyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-ethyl-N-methyl-aminomethyl)-aniline R_f value: 0.3 (silica gel, methylene chloride/methanol=10:1) $C_{27}H_{27}N_3O_3$

ESI mass spectrum: m/z=440 [M−H⁻].

(95) 3-Z-[1-(4-(imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(imidazol-2-yl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{26}H_{20}N_4O_3$

ESI mass spectrum: m/z=435 [M−H⁻].

(96) 3-Z-[1-(4-(1-ethyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1-ethyl-imidazol-2-yl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol=10:1) $C_{28}H_{24}N_4O_3$

ESI mass spectrum: m/z=463 [M−H⁻].

(97) 3-Z-[1-(4-(1-benzyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1-benzyl-imidazol-2-yl)-aniline R_f value: 0.3 (silica gel, methylene chloride/methanol=20:1) $C_{33}H_{26}N_4O_3$

ESI mass spectrum: m/z=525 [M−H⁻].

(98) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-isopropylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(2-dimethylamino-ethyl)-N-isopropylsulphonyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{34}N_4O_5S$

ESI mass spectrum: m/z=561 [M−H⁻].

(99) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(piperidin-1-yl-methylcarbonyl)-N-methyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{31}H_{32}N_4O_4$

ESI mass spectrum: m/z=523 [M−H⁻].

(100) 3-Z-[1-(4-(N-(morpholin-4-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(morpholinyl-methylcarbonyl)-N-methyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{30}N_4O_5$

ESI mass spectrum: m/z=525 [M−H⁻].

(101) 3-Z-[1-(4-(N-((4-benzyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((4-benzyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{37}H_{37}N_5O_4$

ESI mass spectrum: m/z=614 [M−H⁻].

(102) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-methylcarbony)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(pyrrolidin-1-yl-methylcarbonyl)-N-methyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{30}N_4O_4$

ESI mass spectrum: m/z=509 [M−H⁻].

(103) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-bromo-anilino)-1-phenyl-methylene]6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-bromo-aniline R_f value: 0.6 (silica gel, methylene chloride/methanol=5:1) $C_{29}H_{29}BrN_4O_4$

ESI mass spectrum: m/z=575/577 [M−H⁻].

(104) 3-Z-[1-(4-(5-methyl-imidazol-4-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(5-methyl-imidazol-4-yl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol/ammonia=10:1:0.01) $C_{27}H_{22}N_4O_3$

ESI mass spectrum: m/z=449 [M−H⁻].

(105) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((2-dimethylamino-ethyl)-carbonyl)-N-isopropyl-p-phenylenediamine R_f value: 0.1 (silica gel, methylene chloride/methanol=10:1) $C_{31}H_{34}N_4O_4$

ESI mass spectrum: m/z=525 [M−H⁻].

(106) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((2-dimethylamino-ethyl)-carbonyl)-N-benzyl-p-phenylenediamine R_f value: 0.1 (silica gel, methylene chloride/methanol=10:1) $C_{31}H_{34}N_4O_4$

ESI mass spectrum: m/z=525 [M−H⁻].

(107) 3-Z-[1-(4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{33}H_{37}N_3O_5$

ESI mass spectrum: m/z=554 [M−H⁻].

(108) 3-Z-[1-(4-(N-((N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{29}H_{29}N_5O_5$

ESI mass spectrum: m/z=526 [M−H⁻].

(109) 3-Z-[1-(4-(4-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-methyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{34}H_{32}N_4O_4$

ESI mass spectrum: m/z=559 [M−H⁻].

(110) 3-Z-[1-(4-(N-(di-(2-methoxyethyl)-amino-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(di-(2-methoxyethyl)-amino-methylcarbonyl)-N-methyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{32}H_{36}N_4O_6$

ESI mass spectrum: m/z=571 [M−H⁻].

(111) 3-Z-[1-(4-(N-((2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-p-phenylenediamine R_f value: 0.8 (silica gel, methylene chloride/methanol=5:1) $C_{36}H_{41}N_5O_6$

ESI mass spectrum: m/z=638 [M−H⁻].

(112) 3-Z-[1-(4-(N-((2-(piperidin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((2-(piperidin-1-yl)-ethyl)-carbonyl)-N-methyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=5:1) $C_{32}H_{34}N_4O_4$

ESI mass spectrum: m/z=537 [M−H⁻].

(113) 3-Z-[1-(4-(N-((2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl)-N-methyl-p-phenylenediamine R_f value: 0.4 (silica gel, methylene chloride/methanol=10:1) $C_{35}H_{34}N_4O_4$

ESI mass spectrum: m/z=573 [M−H⁻].

(114) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(dimethylaminomethylcarbonyl)-N-isopropyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{32}N_4O_4$

ESI mass spectrum: m/z=511 [M−H⁻].

(115) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{33}H_{36}N_4O_4$

ESI mass spectrum: m/z=551 [M−H⁻].

(116) 3-Z-[1-(4N-((4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl)-N-isopropyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{37}H_{43}N_5O_6$

ESI mass spectrum: m/z=652 [M−H⁻].

(117) 3-Z-[1-(4-(N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-benzyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{40}H_{36}N_4O_4$

ESI mass spectrum: m/z=635 [M−H⁻].

(118) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and N-(dimethylaminomethyl-carbonyl)-N-benzyl-p-phenylenediamine R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{34}H_{32}N_4O_4$

ESI mass spectrum: m/z=559 [M−H⁻].

(119) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(5-methyl-imidazol-4-yl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{37}H_{36}N_4O_4$

ESI mass spectrum: m/z=559 [M−H⁻].

(120) 3-Z-[1-(4-(1,2,4-triazol-2-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1,2,4-triazol-1-yl-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{26}H_{21}N_5O_3$

ESI mass spectrum: m/z=450 [M−H⁻].

(121) 3-Z-[1-(4-(1,2,3-triazol-2-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1,2,3-triazol-2-yl-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=20:1) $C_{26}H_{21}N_5O_3$

ESI mass spectrum: m/z=450 [M−H⁻].

(122) 3-Z-[1-(4-(1,2,3-triazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(1,2,3-triazol-1-yl-methyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol=9:1) $C_{26}H_{21}N_5O_3$

ESI mass spectrum: m/z=450 [M−H⁻].

(123) 3-Z-[1-(4-((N-aminocarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-aminocarbonylmethyl-N-methyl-amino)-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{27}H_{26}N_4O_4$

ESI mass spectrum: m/z=469 [M−H⁻].

(124) 3-Z-[1-(4-((di-(2-methoxy-ethyl)-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((di2-methoxy-ethyl)-amino)-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{33}N_3O_5$

ESI mass spectrum: m/z=514 [M−H⁻].

(125) 3-Z-[1-(4-(pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(pyrrolidin-1-yl-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{28}H_{27}N_3O_3$

ESI mass spectrum: m/z=452 [M−H⁻].

(126) 3-Z-[1-(4-((di-(2-hydroxy-ethyl)-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((di-(2-hydroxy-ethyl)-amino)-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{28}H_{29}N_3O_5$

ESI mass spectrum: m/z=486 [M−H⁻].

(127) 3-Z-[1-(4-((N-ethoxycarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-ethoxycarbonylmethyl-N-methyl-amino)-methyl)-aniline R_f value: 0.5 (aluminium oxide, methylene chloride/ethanol=40:1) $C_{29}H_{29}N_3O_5$

ESI mass spectrum: m/z=498 [M−H⁻].

(128) 3-Z-[1-(4-(azetidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(azetidin-1-yl-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol/ammonia=9:1:0.5) $C_{27}H_{25}N_3O_3$

ESI mass spectrum: m/z=438 [M−H⁻].

(129) 3-Z-[1-(4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{32}H_{35}N_3O_5$

ESI mass spectrum: m/z=540 [M−H⁻].

(130) 3-Z-[1-(4-((N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl)-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{33}N_3O_5$

ESI mass spectrum: m/z=514 [M−H⁻].

(131) 3-Z-[1-(4-((N-(tert.butoxycarbonyl-3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(N-tert.butoxycarbonyl-3-amino-propyl)-N-methyl-

aminomethyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{33}H_{38}N_4O_5$

ESI mass spectrum: m/z=571 [M+H$^+$].

(132) 3-Z-[1-(4-((N-(methylcarbamoyl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-(methylcarbamoyl-methyl)-N-methyl-amino)-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{28}H_{28}N_4O_4$

ESI mass spectrum: m/z=483 [M–H$^-$].

(133) 3-Z-[1-(4-((N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl)-aniline R_f value: 0.3 (silica gel, methylene chloride/methanol=10:1) $C_{29}H_{30}N_4O_4$

ESI mass spectrum: m/z=497 [M–H$^-$].

(134) 3-Z-[1-(4-methyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-methyl-aniline R_f value: 0.4 (silica gel, methylene chloride/methanol=9:1) $C_{24}H_{20}N_2O_3$

ESI mass spectrum: m/z=383 [M–H$^-$].

(135) 3-Z-[1-(4-((N-propyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-propyl-N-methyl-amino)-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol 9:1) $C_{28}H_{29}N_3O_3$

ESI mass spectrum: m/z=454 [M–H$^-$].

(136) 3-Z-[1-(4-((N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl)-aniline R_f value: 0.5 (aluminium oxide, methylene chloride/ethanol=40:1) $C_{27}H_{27}N_3O_4$

ESI mass spectrum: m/z=456 [M–H$^-$].

(137) 3-Z-[1-(4-((N-(2-dimethylaminoethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(N-(2-dimethylamino-ethyl)-N-methyl-amino)-methyl)-aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{29}H_{32}N_4O_3$

ESI mass spectrum: m/z=483 [M–H$^-$].

(138) 3-Z-[1-(4-((N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-((N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl)-aniline aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{34}N_4O_3$

ESI mass spectrum: m/z=497 [M–H$^-$].

(139) 3-Z-[1-(4-(3-oxo-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 1-acetyl-3-(1-ethoxy-1-phenylmethylene)-6-methoxycarbonyl-2-indolinone and 4-(3-oxo-piperazin-1-yl-methyl)-aniline aniline R_f value: 0.46 (silica gel, methylene chloride/methanol=9:1) $C_{28}H_{26}N_4O_4$

ESI mass spectrum: m/z=481 [M–H$^-$].

EXAMPLE 4

3-Z-[1-(4-carboxy-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone

485 mg of 3-Z-[1-(4-tert.butoxycarbonyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone are dissolved in 15 ml of methylene chloride and 6.0 ml of trifluoroacetic acid are added. The mixture is stirred for 2 hours at room temperature. Then the solvent is removed and the residue recrystallised from ether.

Yield: 375 mg (87% of theory), R_f value: 0.3 (silica gel, methylene chloride/methanol=10:1) $C_{25}H_{20}N_2O_5$

Mass spectrum: m/z=428 [M$^+$].

The following compounds are prepared analogously to Example 4:

(1) 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.5 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01) $C_{24}H_{21}N_3O_3$

ESI mass spectrum: m/z=398 [M–H$^-$].

(2) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.4 (silica gel, methylene chloride/methanol/ammonia=10:1:0.01) $C_{25}H_{25}N_3O_3$

ESI mass spectrum: m/z=426 [M–H$^-$].

(3) 3-Z-[1-(4-carboxymethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-tert.butoxycarbonylmethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone R_f value: 0.1 (aluminium oxide, methylene chloride/ethanol/ammonia=5: 1:0.01) $C_{26}H_{22}N_2O_5$

ESI mass spectrum: m/z=441 [M–H$^-$].

(4) 3-Z-[1-(4-carboxy-anilino)-1-ethyl-methylene)-6-ethoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-tert.butoxycarbonyl-anilino)-1-ethyl-methylene]-6-ethoxycarbonyl-2-indolinone R_f value: 0.1 (aluminium oxide, methylene chloride/ethanol=20:1) $C_{21}H_{20}N_2O_5$

ESI mass spectrum: m/z=379 [M–H$^-$].

(5) 3-Z-[1-(4-(piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.1 (silica gel, methylene chloride/methanol/ammonia=10:1:0.01) $C_{28}H_{28}N_4O_3$

ESI mass spectrum: m/z=469 [M+H$^+$].

(6) 3-Z-[1-(4-butylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{28}H_{29}N_3O_3$

ESI mass spectrum: m/z=454 [M–H$^-$].

(7) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]6-ethoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-N-ethyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone R_f value: 0.3 (silica gel, methylene chloride/methanol/ammonia=10:1:0.01) $C_{27}H_{27}N_3O_3$

ESI mass spectrum: m/z=442 [M+H$^+$].

(8) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone R_f value: 0.2 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01) $C_{25}H_{24}N_4O_2$

ESI mass spectrum: m/z=411 [M–H$^-$].

(9) 3-Z-[1-(4-(N-(piperazin-1-yl-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-(4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.35 (silica gel, methylene chloride/methanol=9:1) $C_{32}H_{35}N_5O_4$

ESI mass spectrum: m/z=552 [M–H$^-$].

(10) 3-Z-[1-(4-(N-((2-(piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-((2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.4 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01) $C_{31}H_{33}N_5O_4$

ESI mass spectrum: m/z=540 [M+H$^+$].

(11) 3-Z-[1-(4-(N-propyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.35 (silica gel, methylene chloride/methanol=9:1) $C_{27}H_{27}N_3O_3$

ESI mass spectrum: m/z=440 [M–H$^-$].

(12) 3-Z-[1-(4-((N-(3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-((N-(tert.butoxycarbonyl-3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.35 (silica gel, methylene chloride/methanol=9:1) $C_{28}H_{30}N_4O_3$

ESI mass spectrum: m/z=471 [M+H$^+$].

EXAMPLE 5

3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

100 mg of 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone are dissolved in 20 ml of ethanol, 0.2 ml of 1N hydrochloric acid are added and the mixture is hydrogenated for 70 minutes at room temperature and 50 psi hydrogen pressure. The reaction solution is filtered and the filtrate concentrated by rotary evaporation. The residue is dried in vacuo at 100° C.

Yield: 50 mg (53% of theory), R_f value: 0.3 (silica gel, methylene chloride/ethanol/ammonia=5:1:0.01) $C_{26}H_{25}N_3O_3$

ESI mass spectrum: m/z=426 [M–H$^-$].

The following compounds are prepared analogously to Example 5:

(1) 3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.2 (silica gel, methylene chloride/methanol/ammonia=10:1:0.01) $C_{25}H_{23}N_3O_3$

ESI mass spectrum: m/z=412 [M–H$^-$].

(2) 3-Z-[1-(4-(N-(2-methylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-((2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f Value: 0.3 (silica gel, methylene chloride/methanol/ammonia=10:1:0.01) $C_{27}H_{28}N_4O_5S$

ESI mass spectrum: m/z=519 [M–H$^-$].

(3) 3-Z-[1-(4N-(2-amino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-cyanomethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.5 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01) $C_{26}H_{26}N_4O_5S$

ESI mass spectrum: m/z=505 [M–H$^-$].

(4) 3-Z-[1-(4-(N-(3-methylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-(3-N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.3 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01) $C_{28}H_{30}N_4O_5S$

ESI mass spectrum: m/z=533 [M–H$^-$].

(5) 3-Z-[1-(4-(N-(piperazin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-((4-benzyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.5 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{31}N_5O_4$

ESI mass spectrum: m/z=524 [M–H$^-$].

(6) 3-Z-[1-(4-(N-(methylamino-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.3 (silica gel, methylene chloride/methanol=9:1) $C_{27}H_{26}N_4O_4$

ESI mass spectrum: m/z=469 [M–H$^-$].

(7) 3-Z-[1-(4-(N-((2-methylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-((2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.3 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01) $C_{28}H_{28}N_4O_4$

ESI mass spectrum: m/z=483 [M−H⁻].

EXAMPLE 6

3-Z-[1-(4-ureidomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

300 mg of 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone are dissolved in 15 ml of methanol and 200 ml of triethylamine are added. Then 400 mg of potassium cyanate in 5 ml of water are added. After 2 days of stirring at room temperature the reaction solution is concentrated by rotary evaporation, the residue taken up in methylene chloride and washed once with water and once with saturated sodium chloride solution. The organic phase is dried over sodium sulphate and concentrated by rotary evaporation. The residue is dried in vacuo at 100° C.

Yield: 100 mg of (21% of theory), R_f value: 0.7 (silica gel, methylene chloride/methanol=5;1) $C_{25}H_{22}N_4O_4$

ESI mass spectrum: m/z=441 [M−H⁻].

EXAMPLE 7

3-Z-[1-(4-guanidinomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

300 mg of 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone are dissolved in 5 ml of dimethylformamide and 300 ml of triethylamine are added. Then 700 mg of 3,5-dimethylpyrazol-1-carboxylic acid amidine in 5 ml of dimethylformamide are added. After one day of stirring at room temperature the reaction solution is concentrated by rotary evaporation. The residue is dried at 100° C. in vacuo.

Yield: 200 mg (87% of theory), R_f value: 0.1 (Reversed phase RP 8, methanol/five percent saline solution=6:4) $C_{25}H_{23}N_5O_3$

Mass spectrum: m/z=441 [M⁺].

EXAMPLE 8

3-Z-[1-(4-acetylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

100 mg of 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone are dissolved in 5 ml of glacial acetic acid, 0.1 ml of acetic anhydride is added and the mixture is stirred for 10 minutes at room temperature. After this time the reaction solution is poured onto saturated soda solution and extracted four times with methylene chloride. The combined organic phases are washed with saturated saline solution, dried over sodium sulphate and concentrated by rotary evaporation. The residue is dried at 100° C. in vacuo.

Yield: 20 mg (23% of theory), R_f value: 0.4 (silica gel, methylene chloride/methanol=10:1) $C_{26}H_{23}N_3O_4$

ESI mass spectrum: m/z 440 [M−H⁻].

The following compounds are prepared analogously to Example 8:

(1) 3-Z-[1-(4-(N-methylsulphonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and methanesulphonyl chloride/triethylamine R_f value: 0.7 (silica gel, methylene chloride/methanol=5:1) $C_{25}H_{23}N_3O_5S$

ESI mass spectrum: m/z=476 [M−H⁻].

(2) 3-Z-[1-(4-(4-benzoyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and benzoyl chloride R_f value: 0.7 (silica gel, methylene chloride/methanol=10:1) $C_{35}H_{32}N_4O_4$

ESI mass spectrum: m/z=571 [M−H⁻].

(3) 3-Z-[1-(4-((N-(3-acetylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-((N-(3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.3 (silica gel, methylene chloride/methanol=9:1) $C_{30}H_{32}N_4O_4$

ESI mass spectrum: m/z=511 [M−H⁻].

EXAMPLE 9

3-Z-(1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

0.8 g of 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone are dissolved in 30 ml of ethanol, 8.3 ml of 1N sodium hydroxide solution are added and the mixture is stirred for 1 hour at 80° C. After cooling, it is neutralised with 8.3 ml of 1N hydrochloric acid. The precipitate formed is suction filtered, washed with water, ethanol and ether and dried in vacuo at 100° C.

Yield: 0.7 g of (89% of theory), R_f value: 0.2 (silica gel, methylene chloride/methanol=5:2) $C_{28}H_{27}N_3O_3$

Mass spectrum: m/z=453 [M⁺].

The following compounds are prepared analogously to Example 9:

(1) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone R_f value: 0.4 (silica gel, toluene/ethyl acetate=5:1) $C_{22}H_{15}BrN_2O_3$

ESI mass spectrum: m/z=435/437 [M+H⁺].

(2) 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone R_f value: 0.7 (Reversed phase RP 8, methanol/five percent saline solution=4:1) $C_{25}H_{23}N_3O_3$

ESI mass spectrum: m/z=414 [M+H⁺].

(3) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone R_f value: 0.7 (Reversed phase RP 8, methanol/five percent saline solution=4:1) $C_{25}H_{23}N_3O_3$

ESI mass spectrum: m/z=412 [M−H⁻].

(4) 3-Z-[1-(4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-[(2,6-dimethyl-piperidin-1-yl)-methyl]-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-

indolinone R_f value: 0.6 (Reversed phase RP 8, methanol/five percent saline solution=4:1) $C_{30}H_{31}N_3O_3$

ESI mass spectrum: m/z=482 [M+H$^+$].

(5) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.6 (Reversed phase RP 8, methanol/five percent saline solution=4:1) $C_{26}H_{20}N_4O_3$

ESI mass spectrum: m/z=435 [M–H$^-$].

(6) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.3 (silica gel, methylene chloride/methanol=10:1) $C_{28}H_{26}N_4O_5$

ESI mass spectrum: m/z=497 [M–H$^-$].

(7) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.6 (Reversed phase RP 8, methanol/five percent saline solution=4:1) $C_{25}H_{23}N_3O_3$

ESI mass spectrum: m/z=412 [M–H$^-$].

(8) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone R_f value: 0.6 (Reversed phase RP 8, methanol/five percent saline solution=4:1) $C_{27}H_{26}N_4O_4$

ESI mass spectrum: m/z=469 [M–H$^-$].

(9) 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone R_f value: 0.4 (silica gel, methylene chloride/methanol=10:1) $C_{30}H_{31}N_3O_5$

ESI mass spectrum: m/z=512 [M–H$^-$].

(10) 3-Z-[1-(4-((N-carboxymethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-((N-ethoxycarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl -2-indolinone R_f value: 0.4 (silica gel, methylene chloride/methanol=6:1) $C_{27}H_{25}N_3O_5$

ESI mass spectrum: m/z=470 [M–H$^-$].

EXAMPLE 10

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

0.9 g of 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone are suspended in 35 ml of dimethylformamide and 0.4 g of carbonyldiimidazole are added. The mixture is stirred for 14 hours at 80° C. After this time 20 ml of methanol are added and the mixture is stirred for another 3 hours at 50° C. The solvent is removed and the residue is purified over a silica gel column with methylene chloride/methanol (3:1) as eluant.

Yield: 0.5 g of (49% of theory), R_f value: 0.5 (aluminium oxide, methylene chloride/methanol=30:1) $C_{29}H_{29}N_3O_3$

ESI mass spectrum: m/z=468 [M+H$^+$].

The following compounds are prepared analogously to Example 10:

(1) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-benzyloxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and benzyl alcohol R_f value: 0.6 (aluminium oxide, methylene chloride/methanol=30:1) $C_{35}H_{33}N_3O_3$

Mass spectrum: m/z=543 [M$^+$].

(2) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-isopropyloxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and isopropanol R_f value: 0.4 (aluminium oxide, methylene chloride/isopropanol=30:1) $C_{31}H_{33}N_3O_3$

Mass spectrum: m/z=495 [M$^+$].

(3) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-propyloxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and n-propanol R_f value: 0.7 (silica gel, methylene chloride/methanol=5:1) $C_{31}H_{33}N_3O_3$

Mass spectrum: m/z=495 [M$^+$].

(4) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-butyloxycarbonyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and n-butanol R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{32}H_{35}N_3O_3$

Mass spectrum: m/z=509 [M$^+$].

(5) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and ammonia R_f value: 0.5 (silica gel, methylene chloride/methanol=10:1) $C_{22}H_{16}BrN_2O_3$

Mass spectrum: m/z=432/434 [M–H$^-$].

(6) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethylcarbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and ethylamine gas R_f value: 0.6 (silica gel, methylene chloride/methanol=5:1) $C_{30}H_{32}N_4O_2$

Mass spectrum: m/z=480 [M$^+$].

(7) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-methoxy-ethoxy)-carbonyl]-2-indolinone

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and methylglycol R_f value: 0.8 (silica gel, methylene chloride/methanol=4:1) $C_{25}H_{23}N_3O_3$

ESI mass spectrum: m/z=470 [M–H$^-$].

(8) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-dimethylamino-ethoxy)-carbonyl]-2-indolinone

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and 2-dimethylaminoethanol aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=5:2) $C_{29}H_{32}N_4O_3$

ESI mass spectrum: m/z=483 [M–H$^-$].

(9) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-N-tert.butoxycarbonyl-amino-ethoxy)-carbonyl]-2-indolinone

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and 2-N-tert.butoxycarbonyl-amino-ethanol aniline R_f value: 0.8 (silica gel, methylene chloride/methanol=5:2) $C_{32}H_{36}N_4O_5$

ESI mass spectrum: m/z=412 [M−H⁻].

(10) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2,2,2-trifluoroethoxy)-carbonyl]-2-indolinone

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and 2,2,2-trifluoroethanol aniline R_f value: 0.5 (silica gel, methylene chloride/methanol=5:1) $C_{27}H_{24}F_3N_3O_3$

ESI mass spectrum: m/z=494 [M−H⁻].

EXAMPLE 11

3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

0.9 g of 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone, 0.8 g of TBTU and 0.4 g of HOBT are suspended in 25 ml of dimethylformamide and 1.0 ml of triethylamine are added. The mixture is stirred for 15 minutes at room temperature. After this time ammonia gas is introduced at 10–15° C. over a period of 15 minutes and the mixture is stirred for 1.5 hours at room temperature. The precipitate formed is suction filtered, washed with water, ethanol and ether and dried at 100° C. in vacuo.

Yield: 0.6 g (64% of theory), R_f value: 0.4 (Reversed phase RP 8, methanol/five percent saline solution=6:4) $C_{28}H_{28}N_4O_2$

ESI mass spectrum: m/z=453 [M+H⁺].

The following compounds are prepared analogously to Example 11:

(1) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-dimethylcarbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and dimethylamine hydrochloride/diisopropylethylamine R_f value: 0.5 (silica gel, methylene chloride/methanol=5:1) $C_{30}H_{32}N_4O_2$

ESI mass spectrum: m/z=481 [M+H⁻].

(2) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-(N-ethyl-N-methyl-carbamoyl)-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and N-ethyl-N-methyl-amine R_f value: 0.5 (aluminium oxide, methylene chloride/ethanol=20:1) $C_{31}H_{34}N_4O_2$

ESI mass spectrum: m/z=495 [M+H⁺].

(3) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methylcarbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and methylamine hydrochloride/diisopropylethylamine R_f value: 0.3 (aluminium oxide, methylene chloride/ethanol=20:1) $C_{29}H_{30}N_4O_2$

ESI mass spectrum: m/z=467 [M+H⁺].

(4) 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methylcarbamoyl-2-indolinone

Prepared from 3-Z-[1-(3-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxyl-2-indolinone and methylamine hydrochloride/triethylamine R_f value: 0.3 (silica gel, methylene chloride/ethanol=2:1) $C_{26}H_{26}N_4O_2$

Mass spectrum: m/z=426 [M⁺].

(5) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-(2-hydroxyethyl-carbamoyl)-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and ethanolamine/diisopropylethylamine R_f value: 0.5 (aluminium oxide, methylene chloride/methanol=20:1) $C_{30}H_{32}N_4O_3$

ESI mass spectrum: m/z=495 [M−H⁻].

(6) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-diethylcarbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone and diethylamine hydrochloride/diisopropylethylamine R_f value: 0.8 (aluminium oxide, methylene chloride/methanol=10:1) $C_{32}H_{36}N_4O_2$

ESI mass spectrum: m/z=509 [M+H⁺].

(7) 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-tert.butoxycarbonyl-ethylaminomethyl)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone R_f value: 0.3 (silica gel, toluene/ethyl acetate/ethanol=4:2:1) $C_{30}H_{32}N_4O_4$

ESI mass spectrum: m/z=511 [M−H⁻].

(8) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone

Prepared from 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-carboxy-2-indolinone R_f value: 0.5 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01) $C_{27}H_{27}N_5O_3$

ESI mass spectrum: m/z=468 [M−H⁻].

EXAMPLE 12

3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone x citric acid

3.25 g of citric acid monohydrate are placed in 50 ml of methanol and 5.0g of 3-Z-[1-(4-(N-dimethylaminomethyl-carbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone are added at room temperature. The solution formed is evaporated down, the residue is washed with ether and recrystallised from ethyl acetate.

Yield: 6.3 g (90% of theory), R_f value: 0.6 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01)

Melting point: 198° C. $C_{28}H_{28}N_4O_5xC_6H_8O_7$.

ESI mass spectrum: m/z=483 [M−H⁻].

Elemental analysis: calc.: C 60.34 H 5.37 N 8.28; found: 59.98 5.25 8.13.

The following compound is prepared analogously to Example 12:

(1) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone x methanesulphonic acid

Prepared from 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and methanesulphonic acid R_f value: 0.6 (silica gel, methylene chloride/methanol/ammonia=5:1:0.01)

Melting point: 275° C. $C_{26}H_{25}N_3O_3xCH_4O_3S$

ESI mass spectrum: m/z=426 [M−H⁻].

Elemental analysis: calc.: C 61.92 H 5.59 N 8.03 S 6.12; found: 61.43 5.87 7.85 5.39.

The following compounds may be prepared analogously to the foregoing Examples:

(1) 3-Z-(1-anilino-1-phenyl-methylene)-6-ethoxycarbonyl-2-indolinone

(2) 3-Z-[1-(4-nitro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(3) 3-Z-[1-(4-fluoro-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone

(4) 3-Z-[1-(4-chloro-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone

(5) 3-Z-[1-(4-iodo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(6) 3-Z-[1-(4-cyano-anilino)-1-phenyl-methylene]-6-ethoxy-carbonyl-2-indolinone

(7) 3-Z-[1-(4-methoxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(8) 3-Z-[1-(4-ethoxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(9) 3-Z-[1-(4-trifluoromethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(10) 3-Z-[1-(4-methyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(11) 3-Z-[1-(4-methylmercapto-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(12) 3-Z-[1-(4-aminomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(13) 3-Z-[1-(4-(isopropylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(14) 3-Z-[1-(4-(anilinomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(15) 3-Z-[1-(4-(propylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(16) 3-Z-[1-(4-(butylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(17) 3-Z-[1-(4-(isobutylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(18) 3-Z-[1-(4-(cyclohexylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(19) 3-Z-[1-(4-(benzylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(20) 3-Z-[1-(4-((N-ethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(21) 3-Z-[1-(4-((N-methyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(22) 3-Z-[1-(4-((N-isopropyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(23) 3-Z-[1-(4-((N-ethyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(24) 3-Z-[1-(4-((N-ethyl-N-isopropyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(25) 3-Z-[1-(4-(dipropylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(26) 3-Z-[1-(4-(diisopropylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(27) 3-Z-[1-(4-((N-benzyl-N-ethyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(28) 3-Z-[1-(4-(dibenzylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(29) 3-Z-[1-(4-(3,6-dihydro-2H-pyridin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(30) 3-Z-[1-(4-(3,5-dimethyl-piperidin-1-y-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(31) 3-Z-[1-(4-(azepan-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(32) 3-Z-[1-(4-(piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(33) 3-Z-[1-(4-(morpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(34) 3-Z-[1-(4-(thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(35) 3-Z-[1-(4-(1-oxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(36) 3-Z-[1-(4-(1,1-dioxo-thiomorpholin-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(37) 3-Z-[1-(4-(acetylamino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(38) 3-Z-[1-(4-(2-amino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(39) 3-Z-[1-(4-(2-methylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(40) 3-Z-[1-(4-(2-ethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(41) 3-Z-[1-(4-(2-diethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(42) 3-Z-[1-(4-(2-piperidin-1-yl-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(43) 3-Z-[1-(4-(2-acetylamino-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(44) 3-Z-[1-(4-(3-amino-propyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(45) 3-Z-[1-(4-(3-dimethylamino-propyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(46) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(47) 3-Z-[1-(4-(N-methylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(48) 3-Z-[1-(4-(N-ethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(49) 3-Z-[1-(4-(N-diethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(50) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(51) 3-Z-[1-(4-(N-(morpholin-4-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(52) 3-Z-[1-(4-(N-(piperazin-1-yl-methylcarbonyl)-N-methyl-amino]-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(53) 3-Z-[1-(4-(N-(2-amino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(54) 3-Z-[1-(40-(2-methylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(55) 3-Z-[1-(4-(N-(2-diethylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(56) 3-Z-[1-(4-(N-acetyl-N-(2-aminoethyl)-amino)-anilino)-1-phenyl-methylene]6-ethoxycarbonyl-2-indolinone

(57) 3-Z-[1-(4-(N-acetyl-N-(2-methylamino-ethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(58) 3-Z-[1-(4-(N-acetyl-N-(2-methylamino-propyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(59) 3-Z-[1-(4-(N-acetyl-N-(2-piperidin-1-yl-ethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(60) 3-Z-[1-(4-(N-acetyl-N-(aminocarbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(61) 3-Z-[1-(4-(N-acetyl-N-(dimethylaminocarbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(62) 3-Z-[1-(4-(N-acetyl-N-(piperidin-1-yl-carbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(63) 3-Z-[1-(4-(N-methyl-N-(aminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(64) 3-Z-[1-(4-(N-methyl-N-methylaminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(65) 3-Z-[1-(4-(N-methyl-N-(dimethylaminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(66) 3-Z-[1-(4-(N-methyl-N-(piperidin-1-yl-carbonyl)-amino)-anilino)-1-phenyl-3-methylene]-6-ethoxycarbonyl-2-indolinone

(67) 3-Z-[1-(4-(N-(2-aminoethyl)-N-methlysulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(68) 3-Z-[1-(4-(N-(2-methylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(69) 3-Z-[1-(4-(N-(2-thylamino-ethyl)-N-methylsulphonyln-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(70) 3-Z-[1-(4-(N-(2-diethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(71) 3-Z-[1-(4-(N-(2-pyrrolidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(72) 3-Z-[1-(4-(N-(2-piperidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(73) 3-Z-[1-(4-(N-(2-piperazin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(74) 3-Z-[1-(4-(N-(2-(morpholin-4-yl)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(75) 3-Z-[1-(4-(N-(aminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(76) 3-Z-[1-(4-(N-(methylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(77) 3-Z-[1-(4-(N-(ethylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(78) 3-Z-[1-(4-(N-(N-(2-dimethylamino-ethyl)-N-methyl-amino)-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(79) 3-Z-[1-(4-(N-(diethylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(80) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(81) 3-Z-[1-(4-(N-(piperidin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(82) 3-Z-[1-(4-(N-(piperazin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(83) 3-Z-[1-(4-(N-((morpholin-4-yl)-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(84) 3-Z-[1-(4-(2-dimethylamino-ethoxy)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(85) 3-Z-[1-(4-(3-dimethylamino-propoxy)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(86) 3-Z-[1-(4-(aminocarbonylmethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(87) 3-Z-[1-(4-(2-aminocarbonyl-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(88) 3-Z-[1-(4-(pyridin-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(89) 3-Z-[1-(4-(pyridine-3-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(90) 3-Z-[1-(4-pyridin-4-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(91) 3-Z-[1-(4-(N-acetyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(92) 3-Z-[1-(4-(N-ethylcarbonyl-N-(dimethylaminocarbonyl-methyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(93) 3-Z-[1-(carbamoylmethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(94) 3-Z-[1-(4-dimethylcarbamoylmethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(95) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

(96) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

(97) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone

(98) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

(99) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-ethylidene]-6-ethoxycarbonyl-2-indolinone

(100) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

(101) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone

(102) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

(103) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

(104) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone

(105) 3-Z-[1-(4-tetrazol-5-yl-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

(106) 3-Z-[1-(4-tetrazol-5-yl-anilino)-ethylidene]-6-ethoxycarbonyl-2-indolinone
(107) 3-Z-[1-(4-tetrazol-5-yl-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone
(108) 3-Z-[1-(4-tetrazol-5-yl-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone
(109) 3-Z-[1-(4-carboxy-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone
(110) 3-Z-[1-(4-carboxy-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone
(111) 3-Z-[1-(4-carboxy-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinon
(112) 3-Z-[1-(4-(N-(3-dimethylamino-propionyl)-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(113) 3-Z-[1-(4-(N-(4-dimethylamino-butyryl)-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(114) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-(2-dimethylamino-ethylsulphonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(115) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-(3-dimethylamino-propylsulphonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(116) 3-Z-[1-(4-((2-hydroxy-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(117) 3-Z-[1-(4-((2-methoxy-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(118) 3-Z-[1-(4-((2-dimethylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(119) 3-Z-[1-(4-((3-dimethylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(120) 3-Z-[1-(4-((N-tert.butoxycarbonyl-2-amino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(121) 3-Z-[1-(4-((N-tert.butoxycarbonyl-3-amino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(122) 3-Z-[1-(4-((2-amino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(123) 3-Z-[1-(4-((3-amino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(124) 3-Z-[1-(4-((2-acetylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(125) 3-Z-[1-(4-((3-acetylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(126) 3-Z-[1-(4-((2-methylsulphonylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(127) 3-Z-[1-(4-((3-methylsulphonylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(128) 3-Z-[1-(4-(N-(N-tert.butoxycarbonyl-2-amino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(129) 3-Z-[1-(4-(N-(2-amino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(130) 3-Z-[1-(4-(N-(2-acetylamino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(131) 3-Z-[1-(4-(N-(2-methylsulphonylamino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(132) 3-Z-[1-(4-(carboxymethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(133) 3-Z-[1-(4-(ethoxycarbonylmethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(134) 3-Z-[1-(4-(carbamoylmethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(135) 3-Z-[1-(4-(dimethylcarbamoyl-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(136) 3-Z-[1-(4-(methylcarbamoyl-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(137) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(138) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-nitro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(139) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-acetylamino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(140) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methylsulphonylamino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(141) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-cyano-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(142) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-hydroxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(143) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methoxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(144) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-ethoxycarbonyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(145) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-carboxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(146) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-carbamoyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(147) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-chloro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(148) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-fluoro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(149) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-bromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(150) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(151) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-trifluoromethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(152) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3,5-dibromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(153) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3,5-dichloro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(154) 3-Z-[1-(4-(dimethylaminomethyl)-3-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone
(155) 3-Z-[1-(4-(dimethylaminomethyl)-3-nitro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(156) 3-Z-[1-(4-(dimethylaminomethyl)-3-acetylamino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(157) 3-Z-[1-(4-(dimethylaminomethyl)-3-(methylsulphonylamino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(158) 3-Z-[1-(4-(dimethylaminomethyl)-3-cyano-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(159) 3-Z-[1-(4-(dimethylaminomethyl)-3-hydroxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(160) 3-Z-[1-(4-(dimethylaminomethyl)-3-methoxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(161) 3-Z-[1-(4-(dimethylaminomethyl)-3-(ethoxycarbonyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(162) 3-Z-[1-(4-(dimethylaminomethyl)-3-carboxy-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(163) 3-Z-[1-(4-(dimethylaminomethyl)-3-carbamoyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(164) 3-Z-[1-(4-(dimethylaminomethyl)-3-chloro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(165) 3-Z-[1-(4-(dimethylaminomethyl)-3-fluoro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(166) 3-Z-[1-(4-(dimethylaminomethyl)-3-bromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(167) 3-Z-[1-(4-(dimethylaminomethyl)-3-methyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(168) 3-Z-[1-(4-(dimethylaminomethyl)-3-trifluoromethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(169) 3-Z-[1-(4-(dimethylaminomethyl)-3,5-dibromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(170) 3-Z-[1-(4-(dimethylaminomethyl)-3,5-dichloro-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(171) 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(172) 3-Z-[1-(4-(N-(imidazo-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(173) 3-Z-[1-(4-(N-(phthalimido-2-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(174) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(175) 3-Z-[1-(4-(N-acetylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(176) 3-Z-[1-(4-(N-methylsulphonylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(177) 3-Z-[1-(4-(N-((N-(2-methoxyethyl)-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(178) 3-Z-[1-(4-(N-((N-(2-dimethylaminoethyl)-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(179) 3-Z-[1-(4-(N-((di-(2-hydroxyethyl)-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(180) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

(181) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-ethylidene]-6-ethoxycarbonyl-2-indolinone

(182) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

(183) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone

(184) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-methylene]-6-ethoxycarbonyl-2-indolinone

(185) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-ethylidene]-6-ethoxycarbonyl-2-indolinone

(186) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-propylidene]-6-ethoxycarbonyl-2-indolinone

(187) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-butylidene]-6-ethoxycarbonyl-2-indolinone

(188) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(189) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(190) 3-Z-[1-(4-((imidazolidin-2,4-dion-5-ylidene)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(191) 3-Z-[1-(4-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(192) 3-Z-[1-(4-(N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(193) 3-Z-[1-(4-(2-oxo-pyrrolidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(194) 3-Z-[1-(4-(N-aminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(195) 3-Z-[1-(4-(N-cyanomethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(196) 3-Z-[1-(4-(2-(imidazol-4-yl)-ethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(197) 3-Z-[1-(4-((2-(N-benzyl-N-methyl-amino)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(198) 3-Z-[1-(4-cyclohexylamino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(199) 3-Z-[1-(4-(imidazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(200) 3-Z-[1-(4-(imidazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(201) 3-Z-[1-(N-methyl-piperidine-4-yl-amino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(202) 3-Z-[1-(4-(imidazol-4-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(203) 3-Z-[1-(4-(4-hydroxy-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(204) 3-Z-[1-(4-(4-methoxy-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(205) 3-Z-[1-(4-benzyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(206) 3-Z-[1-(4-(N-(3-trifluoroacetylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(207) 3-Z-[1-(4-(4-tert.butoxycarbonyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(208) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(209) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(210) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(211) 3-Z-[1-(4-((3-(N-benzyl-N-methyl-amino)-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(212) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(213) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-butyryl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(214) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-isobutyryl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(215) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-benzoyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(216) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(217) 3-Z-[1-(4-(4-hydroxymethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(218) 3-Z-[1-(4-(2-(4-hydroxy-piperidin-1-yl)-ethyl)-anilino)-1-phenyl-methylene)-6-ethoxycarbonyl-2-indolinone

(219) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-propylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(220) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-butylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(221) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(222) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(223) 3-Z-[1-(4-((imidazolidin-2,4-dion-5-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(224) 3-Z-[1-(4-((3-hydroxy-pyrrolidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(225) 3-Z-[1-(4-(cyclohexylyl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(226) 3-Z-[1-(4-(cyclohexyl-carbonyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(227) 3-Z-[1-(4-diethylaminomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(228) 3-Z-[1-(4-(N-(n-hexyl)-N-methyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(229) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(furan-2-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(230) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(2-methoxy-benzoyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(231) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(pyridine-3-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(232) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-(phenyl-acetyl)-amino)-anilino)-1-phenyl-methylene]-ethoxycarbonyl-2-indolinone

(233) 3-Z-[1-(4-(imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(234) 3-Z-[1-(4-(1-ethyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(235) 3-Z-[1-(4-(1-benzyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(236) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-isopropylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(237) 3-Z-[1-(4-(N-((4-benzyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(238) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(239) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-3-bromo-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(240) 3-Z-[1-(4-(5-methyl-imidazol-4-yl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(241) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(242) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(243) 3-Z-[1-(4-(N-butyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(244) 3-Z-[1-(4-(N-((N-aminocarbonylmethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(245) 3-Z-[1-(4N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(246) 3-Z-[1-(4-(N-(di-(2-methoxyethyl)-amino-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(247) 3-Z-[1-(4-(N-((2-(4-tert.butoxycarbonyl-piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(248) 3-Z-[1-(4-(N-((2-(piperidin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(249) 3-Z-[1-(4-(N-((2-(N-benzyl-N-methyl-amino)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(250) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(251) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(252) 3-Z-[1-(4-(N-((4-tert.butoxycarbonyl-piperazin-1-yl)-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(253) 3-Z-[1-(4-(N-((N-benzyl-N-methyl-amino)-methylcarbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(254) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(255) 3-Z-[1-(4-(N-(piperidin-1-yl-methylcarbonyl)-N-benzyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(256) 3-Z-[1-(4-(1,2,4-triazol-2-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(257) 3-Z-[1-(4-(1,2,3-triazol-2-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(258) 3-Z-[1-(4-(1,2,3-triazol-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(259) 3-Z-[1-(4-((N-aminocarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(260) 3-Z-[1-(4-((di-(2-methoxy-ethyl)-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(261) 3-Z-[1-(4-((di-(2-hydroxy-ethyl)-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(262) 3-Z-[1-(4-((N-ethoxycarbonylmethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(263) 3-Z-[1-(4-(azetidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(264) 3-Z-[1-(4-(N-propyl-N-tert.butoxycarbonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(265) 3-Z-[1-(4-((N-(2-(2-methoxy-ethoxy)-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(266) 3-Z-[1-(4-((N-(tert.butoxycarbonyl-3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(267) 3-Z-[1-(4-((N-(methylcarbamoyl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(268) 3-Z-[1-(4-((N-(dimethylcarbamoyl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene)]-6-ethoxycarbonyl-2-indolinone

(269) 3-Z-[1-(4-((N-propyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(270) 3-Z-[1-(4-((N-(2-dimethylamino-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(271) 3-Z-[1-(4-((N-(3-dimethylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(272) 3-Z-[1-(4-((N-(2-methoxy-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(273) 3-Z-[1-(4-((N-(2-hydroxy-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(274) 3-Z-[1-(4-((N-(dioxolan-2-yl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(275) 3-Z-[1-(4-(3-oxo-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(276) 3-Z-[1-(4-(piperazin-1-y-methylcarbonyl)-N-isopropyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(277) 3-Z-[1-(4-(N-((2-(piperazin-1-yl)-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(278) 3-Z-[1-(4-((N-(3-amino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(279) 3-Z-[1-(4-(N-(3-methylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(280) 3-Z-[1-(4-Ureidomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(281) 3-Z-[1-(4-guanidinomethyl-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(282) 3-Z-[1-(4-(N-methlysulphonyl-aminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(283) 3-Z-[1-(4-(4-benzoyl-piperazin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(284) 3-Z-[1-(4-((N-(3-acetylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(285) 3-Z-[1-(4-((N-(3-methylsulphonylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(286) 3-Z-[1-(4-((N-carboxymetyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone

(287) 3-Z-(1-anilino-1-phenyl-methylene)-6-methoxycarbonyl-2-indolinone

(288) 3-Z-[1-(4-nitro-anilino)-1-phenyl-methylene]-6-methoxy carbonyl-2-indolinone

(289) 3-Z-[1-(4-fluoro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(290) 3-Z-[1-(4-chloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(291) 3-Z-[1-(4-bromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(292) 3-Z-[1-(4-iodo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(293) 3-Z-[1-(4-cyano-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(294) 3-Z-[1-(4-carboxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(295) 3-Z-[1-(4-methoxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(296) 3-Z-[1-(4-ethoxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(297) 3-Z-[1-(4-trifluoromethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(298) 3-Z-[1-(4-methylmercapto-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(299) 3-Z-[1-(4-(isopropylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(300) 3-Z-[1-(4-(anilinomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(301) 3-Z-[1-(4-(isobutylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(302) 3-Z-[1-(4-(cyclohexylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(303) 3-Z-[1-(4-(benzylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(304) 3-Z-[1-(4-((N-methyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(305) 3-Z-[1-(4-((N-isopropyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(306) 3-Z-[1-(4-((N-ethyl-N-propyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(307) 3-Z-[1-(4-((N-ethyl-N-isopropyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(308) 3-Z-[1-(4-(dipropylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(309) 3-Z-[1-(4-(diisopropylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(310) 3-Z-[1-(4-((N-benzyl-N-ethyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(311) 3-Z-[1-(4-(dibenzylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(312) 3-Z-[1-(4-(3,6-dihydro-2H-pyridin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(313) 3-Z-[1-(4-(3,5-dimethyl-piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(314) 3-Z-[1-(4-(azepan-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(315) 3-Z-[1-(4-(2-amino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(316) 3-Z-[1-(4-(2-methylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(317) 3-Z-[1-(4-(2-ethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(318) 3-Z-[1-(4-(2-dimethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(319) 3-Z-[1-(4-(2-diethylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(320) 3-Z-[1-(4-(2-piperidin-1-yl-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(321) 3-Z-[1-(4-(2-acetylamino-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(322) 3-Z-[1-(4-(3-amino-propyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(323) 3-Z-[1-(4-(3-dimethylamino-propyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(324) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(325) 3-Z-[1-(4-(N-ethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(326) 3-Z-[1-(4-(N-diethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(327) 3-Z-[1-(4-(N-dipropylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(328) 3-Z-[1-(4-(N-((N-ethyl-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(329) 3-Z-[1-(4-(N-((N-ethyl-N-propyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(330) 3-Z-[1-(4-(N-((N-methyl-N-propyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(331) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-ethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(332) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-propyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(333) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-butyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(334) 3-Z-[1-(4-(N-(2-amino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(335) 3-Z-[1-(4-(N-(2-diethylamino-ethylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(336) 3-Z-[1-(4-(N-acetyl-N-(2-aminoethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(337) 3-Z-[1-(4-(N-acetyl-N-(2-methylamino-ethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(338) 3-Z-[-(4-(N-acetyl-N-(3-methylamino-propyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(339) 3-Z-[1-(4-(N-acetyl-N-(2-piperidin-1-yl-ethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(340) 3-Z-[1-(4-(N-acetyl-N-(aminocarbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(341) 3-Z-[1-(4-(N-acetyl-N-(piperidin-1-yl-carbonylmethyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(342) 3-Z-[1-(4-(N-methyl-N-(aminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(343) 3-Z-[1-(4-(N-methyl-N-(methylaminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(344) 3-Z-[1-(4-(N-methyl-N-(dimethylaminocarbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(345) 3-Z-[1-(4-(N-methyl-N-(piperidin-1-yl-carbonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(346) 3-Z-[1-(4-(N-(2-ethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(347) 3-Z-[1-(4-(N-(2-diethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(348) 3-Z-[1-(4-(N-(2-pyrrolidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(349) 3-Z-[1-(4-N-(2-piperidin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(350) 3-Z-[1-(4-(N-(2-piperazin-1-yl-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6methoxycarbonyl-2-indolinone

(351) 3-Z-[1-(4-(N-(2-(4-morpholin-1-yl)-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(352) 3-Z-[1-(4-(N-(ethylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(353) 3-Z-[1-(4-(N-(diethylaminocarbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(354) 3-Z-[1-(4-(N-(pyrrolidin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(355) 3-Z-[1-(4-(N-(piperidin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(356) 3-Z-[1-(4-(N-(piperazin-1-yl-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(357) 3-Z-[1-(4-(N-((morpholin-4-yl)-carbonylmethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(358) 3-Z-[1-(4-(2-dimethylamino-ethoxy)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(359) 3-Z-[1-(4-(3-dimethylamino-propoxy)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(360) 3-Z-[1-(4-(aminocarbonylmethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(361) 3-Z-[1-(4-(2-aminocarbonyl-ethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(362) 3-Z-[1-(4-(pyridin-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(363) 3-Z-[1-(4-(pyridine-3-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(364) 3-Z-[1-(4((N-phenethyl-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(365) 3-Z-[1-(4-(N-acetyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(366) 3-Z-[1-(4-(N-ethylcarbonyl-N-(dimethylaminocarbonyl-methyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(367) 3-Z-[1-(4-(N-methyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(368) 3-Z-[1-(4-carboxymethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(369) 3-Z-[1-(4-carbamoylmethyl-anilino)-1phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(370) 3-Z-[1-(4-dimethylcarbamoylmethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(371) 3-Z-[1-(4-tetrazol-5-yl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(372) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(373) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(374) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

(375) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(376) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(377) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(378) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-propylidede]-6-methoxycarbonyl-2-indolinone

(379) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(380) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsuphony-amino)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(381) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(382) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

(383) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(384) 3-Z-[1-(4-tetrazol-5-yl-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(385) 3-Z-[1-(4-tetrazol-5-yl-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(386) 3-Z-[1-(4-tetrazol-5-yl-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

(387) 3-Z-[1-(4-tetrazol-5-yl-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(388) 3-Z-[1-(4-carboxy-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(389) 3-Z-[1-(4-carboxy-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(390) 3-Z-[1-(4carboxy-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

(391) 3-Z-[1-(4-carboxy-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(392) 3-Z-[1-(4-(N-benzyl-N-methyl-aminomethyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(393) 3-Z-[1-(4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(394) 3-Z-[1-(4-((benzo(1,3)dioxol-5-yl-methyl)-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(395) 3-Z-[1-(4-(N-phenethyl-N-methyl-aminomethyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(396) 3-Z-[1-(4-(N-(3,4-dimethoxy-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(397) 3-Z-[1-(4-(N-(4-Chloro-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(398) 3-Z-[1-(4-(N-(4-methylbenzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(399) 3-Z-[1-(4-(N-(4-fluoro-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(400) 3-Z-[1-(4-(N-(4-bromo-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-methoxycarbonyl-2-indolinone

(401) 3-Z-[1-(4-(N-(3-dimethylamino-propionyl)-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(402) 3-Z-[1-(4-(N-(4-dimethylamino-butyryl)-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(403) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-(2-dimethylamino-ethylsulphonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(404) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-(3-dimethylamino-propylsulphonyl)-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(405) 3-Z-[1-(4-((2-hydroxy-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(406) 3-Z-[1-(4-((2-methoxy-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(407) 3-Z-[1-(4-((2-dimethylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(408) 3-Z-[1-(4-((3-dimethylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(409) 3-Z-[1-(4-((N-tert.butoxycarbonyl-2-amino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(410) 3-Z-[1-(4-((N-tert.butoxycarbonyl-3-amino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(411) 3-Z-[1-(4-((2-amino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(412) 3-Z-[1-(4-((3-amino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(413) 3-Z-[1-(4-((2-acetylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(414) 3-Z-[1-(4-((3-acetylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(415) 3-Z-[1-(4-((2-methylsulphonylamino-ethyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(416) 3-Z-[1-(4-((3-methylsulphonylamino-propyl)-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(417) 3-Z-[1-(4-(N-(N-tert.butoxycarbonyl-2-amino-ethyl)-N-methyl-amino-methyl)-anilino-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(418) 3-Z-[1-(4-(N-(2-amino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(419) 3-Z-[1-(4-(N-(2-acetylamino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(420) 3-Z-[1-(4-(N-(2-methylsulphonylamino-ethyl)-N-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(421) 3-Z-[1-(4-(carboxymethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(422) 3-Z-[1-(4-(ethoxycarbonylmethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(423) 3-Z-[1-(4-(carbamoylmethyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(424) 3-Z-[1-(4-(dimethylcarbamoyl-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(425) 3-Z-[1-(4-(methylcarbamoyl-methyl-amino-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(426) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-amino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(427) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-nitro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(428) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-acetylamino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(429) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methylsulphonylamino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(430) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-cyano-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(431) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-hydroxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(432) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methoxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(433) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-ethoxycarbonyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(434) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-carboxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(435) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-carbamoyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(436) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-chloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(437) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-fluoro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(438) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-bromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(439) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-methyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(440) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3-trifluoromethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(441) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3,5-dibromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(442) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-3,5-dichloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(443) 3-Z-[1-(4-(dimethylaminomethyl)-3-amino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(444) 3-Z-[1-(4-(dimethylaminomethyl)-3-nitro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(445) 3-Z-[1-(4-(dimethylaminomethyl)-3-acetylamino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(446) 3-Z-[1-(4-(dimethylaminomethyl)-3-methylsulphonylamino-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(447) 3-Z-[1-(4-(dimethylaminomethyl)-3-cyano-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(448) 3-Z-[1-(4-(dimethylaminomethyl)-3-hydroxy-anilino)-1-phenyl-methylene]-6-1methoxycarbonyl-2-indolinone

(449) 3-Z-[1-(4-(dimethylaminomethyl)-3-methoxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(450) 3-Z-[1-(4-(dimethylaminomethyl)-3-ethoxycarbonyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(451) 3-Z-[1-(4-(dimethylaminomethyl)-3-carboxy-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(452) 3-Z-[1-(4-(dimethylaminomethyl)-3-carbaroyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(453) 3-Z-[1-(4-(dimethylaminomethyl)-3-chloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(454) 3-Z-[1-(4-(dimethylaminomethyl)-3-fluoro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(455) 3-Z-[1-(4-(dimethylaminomethyl)-3-bromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(456) 3-Z-[1-(4-(dimethylaminomethyl)-3-methyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(457) 3-Z-[1-(4-(dimethylaminomethyl)-3-trifluoromethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(458) 3-Z-[1-(4-dimethylaminomethyl-3,5-dibromo-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(459) 3-Z-[1-(4-(dimethylaminomethyl)-3,5-dichloro-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(460) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-hydroxy-ethoxy)-carbonyl]-2-indolinone

(461) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(ethoxycarbonyl-methoxy)-carbonyl]-2-indolinone

(462) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(carboxy-methoxy)-carbonyl]-2-indolinone

(463) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(carbamoyl-methoxy)-carbonyl]-2-indolinone

(464) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-hydroxy-ethoxy)-carbonyl]-2-indolinone

(465) 3-Z-[1-(4-N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(ethoxycarbonyl-methoxy)-carbonyl]-2-indolinone

(466) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(carboxy-methoxy)-carbonyl]-2-indolinone

(467) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(carbamoyl-methoxy)-carbonyl]-2-indolinone

(468) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-methoxy-ethoxy)-carbonyl]-2-indolinone

(469) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-dimethylamino-ethoxy)-carbonyl]-2-indolinone

(470) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-(N-tert.butoxycarbonyl-amino)-ethoxy)-carbonyl]-2-indolinone

(471) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2-amino-ethoxy)-carbonyl]-2-indolinone

(472) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-[(2,2,2-trifluoroethoxy)-carbonyl]-2-indolinone

(473) 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(474) 3-Z-[1-(4-(N-(imidazo-1-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(475) 3-Z-[1-(4-(N-(phthalimido-2-yl-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(476) 3-Z-[1-(4-(N-aminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(477) 3-Z-[1-(4-(N-acetylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(478) 3-Z-[1-(4-(N-methylsulphonylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(479) 3-Z-[1-(4-(N-((N-(2-methoxyethyl)-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(480) 3-Z-[1-(4-(N-((N-(2-dimethylaminoethyl)-N-methyl-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(481) 3-Z-[1-(4-(N-((di-(2-hydroxyethyl)-amino)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(482) 3-Z-[1-(4-tert.butoxycarbonylmethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(483) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(484) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-Methyl-amino)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(485) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

(486) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(487) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-methylene]-6-methoxycarbonyl-2-indolinone

(488) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-ethylidene]-6-methoxycarbonyl-2-indolinone

(489) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-propylidene]-6-methoxycarbonyl-2-indolinone

(490) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-butylidene]-6-methoxycarbonyl-2-indolinone

(491) 3-Z-[1-(4-tert.butyloxycarbonyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(492) 3-Z-[1-(4-(N-(2-dimethylaminoethyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(493) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(494) 3-Z-[1-(4-(N-methyl-acetylamino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(495) 3-Z-[1-(4-(imidazol-4-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(496) 3-Z-[1-(4-((N-(dioxolan-2-yl-methyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(497) 3-Z-[1-(4-(N-benzyl-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(498) 3-Z-[1-(4-(2,3,4,5-tetrahydro-benzo(d)azepin-3-yl-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(499) 3-Z-[1-(4-((benzo(1,3)dioxol-5-yl-methyl)-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(500) 3-Z-[-(4-(N-phenethyl-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(501) 3-Z-[1-(4-(N-(3,4-dimethoxy-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(502) 3-Z-[1-(4-(N-(4-Chloro-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(503) 3-Z-[1-(4-(N-(4-methyl-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(504) 3-Z-[1-(4-(N-(4-fluoro-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(505) 3-Z-[1-(4-(N-(4-bromo-benzyl)-N-methyl-amino-methyl)-anilino)-1-methyl-methylene]-6-carbamoyl-2-indolinone

(506) 3-Z-[1-(4-((N-(2-methoxy-ethyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

(507) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-[(2-amino-ethoxy)-carbonyl]-2-indolinone

(508) 3-Z-[1-(4-((N-(3-methylsulfonylamino-propyl)-N-methyl-amino)-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone

EXAMPLE 13

Dry Ampoule Containing 75 mg of Active Substance per 10 ml

Composition:

Active substance	75.0 mg
Mannitol	50.0 mg
water for injection	ad 10.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

EXAMPLE 14

Dry Ampoule Containing 35 mg of Active Substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
water for injections	ad 2.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use, the product is dissolved in water for injections.

EXAMPLE 15

Tablet Containing 50 mg of Active Substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 9 mm.

EXAMPLE 16

Tablet Containing 350 mg of Active Substance

Composition:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 12 mm.

EXAMPLE 17

Capsules Containing 50 mg of Active Substance

Composition:

(1) Active substance	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

EXAMPLE 18

Capsules Containing 350 mg of Active Substance

Composition:

(1) Active substance	350.0 mg
(2) Dried maize starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 0 hard gelatine capsules in a capsule filling machine.

EXAMPLE 19

Suppositories Containing 100 mg of Active Substance

1 Suppository Contains:

Active substance	100.0 mg
Polyethyleneglycol (M.W. 1500)	600.0 mg
Polyethyleneglycol (M.W. 6000)	460.0 mg
Polyethylenesorbitan monostearate	840.0 mg
	2,000.0 mg

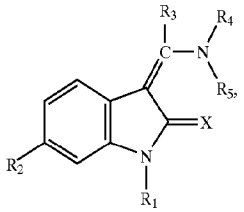
Preparation:

The polyethyleneglycol is melted together with polyethylene sorbitan monostearate. At 40° C. the ground active substance is homogeneously dispersed in the melt. It is cooled to 38° C. and poured into slightly chilled suppository moulds.

What is claimed is:

1. A compound of the formula I

(I)



wherein:

X denotes an oxygen atom,

R_1 denotes a hydrogen atom or a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a carboxy group, a straight-chain or branched C_{1-6}-alkoxy-carbonyl group, a C_{4-7}-cycloalkoxy-carbonyl or an aryloxycarbonyl group,

a straight-chain or branched C_{1-6}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C_{1-3}-alkoxy-carbonyl, aminocarbonyl, C_{1-3}-alkylamino carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a straight-chain or branched C_{2-6}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom or a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group,

R_3 denotes a hydrogen atom, a C_{1-6}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl or heteroaryl group,

a phenyl or naphthyl group, a phenyl or naphthyl group mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group, whilst in the event of disubstitution the substituents may be identical or different and wherein the abovementioned unsubstituted as well as the mono- and disubstituted phenyl and naphthyl groups may additionally be substituted

by a hydroxy, hydroxy-C_{1-3}-alkyl or C_{1-3}-alkoxy-C_{1-3}-alkyl group,

by a cyano, carboxy, carboxy-C_{1-3}-alkyl, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

by a nitro group,

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino or amino—C_{1-3}-alkyl group,

by a C_{1-3}-alkylcarbonylamino, N—(C_{1-3}-alkyl)—C_{1-3}-alkylcarbonylamino, C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl, N—(C_{1-3}-alkyl)—C_{1-3}-alkylcarbonylamino-C_{1-3}-alkyl, C_{1-3}-alkyl-sulphonylamino, C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl, N—(C_{1-3}-alkyl)—C_{1-3}-alkylsulphonylamino-C_{1-3}-alkyl or aryl-C_{1-3}-alkylsulphonylamino group,

by a cycloalkylamino, cycloalkyleneimino, cycloalkyleneiminocarbonyl, cycloalkyleneimino-C_{1-3}-alkyl, cycloalkyleneiminocarbonyl-C_{1-3}-alkyl or cycloalkyleneiminosulphonyl-C_{1-3}-alkyl group having 4 to 7 ring members in each case, whilst in each case the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH or —N(C_{1-3}-alkyl) group,

or by a heteroaryl or heteroaryl-C_{1-3}-alkyl group,

R_4 denotes a C_{3-7}-cycloalkyl group,

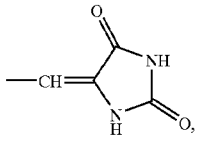
whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group,

or a phenyl group substituted by the group R_6, which may additionally be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-5}-alkyl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, amino, acetylamino, C_{1-3}-alkyl-sulphonylamino, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl, di-(C_{1-3}-alkyl)-aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different and wherein

R_6 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

a cyano, nitro, amino, C_{1-5}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or heteroaryl group,

the group of formula



wherein the hydrogen atoms bound to a nitrogen atom may in each case be replaced independently of one another by a C_{1-3}-alkyl group,

a C_{1-3}-alkoxy group, a C_{1-3}-alkoxy-C_{1-3}-alkoxy, phenyl-C_{1-3}-alkoxy, amino-C_{2-3}-alkoxy, C_{1-3}-alkylamino-C_{2-3}-alkoxy, di-(C_{1-3}-alkyl-amino-C_{2-3}-alkoxy, phenyl-C_{1-3}- alkylamino-C_{2-3}-alkoxy, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}- alkylamino-C_{2-3}-alkoxy, C_{5-7}-cycloalkyleneimino-C_{2-3}-alkoxy or C_{1-3}-alkylmercapto group,

a carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, N—(C_{1-5}-alkyl)—C_{1-3}-alkylaminocarbonyl, phenyl-C_{1-3}-alkylamino-carbonyl, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino-carbonyl, piperazinocarbonyl or N—(C_{1-3}-alkyl)-piperazinocarbonyl group,

a C_{1-3}-alkylaminocarbonyl or N—(C_{1-5}-alkyl)—C_{1-3}-alkylaminocarbonyl group wherein an alkyl moiety is substituted by a carboxy or C_{1-3}-alkoxycarbonyl group or in the 2 or 3 position by a di-(C_{1-3}-alkyl)-amino, piperazino, N—(C_{1-3}-alkyl)-piperazino or a 4- to 7-membered cycloalkyleneimino group,

a C_{3-7}-cycloalkyl-carbonyl group,

wherein the methylene group in the 4 position of the 6- or 7-membered cycloalkyl moiety may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group,

a 4- to 7-membered cycloalkyleneimino group wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

the cycloalkylene moiety may be fused to a phenyl ring or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group,

a C_{1-4}-alkyl group substituted by the group R_7, wherein R_7 denotes a C_{3-7}-cycloalkyl group,

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group or

in a 5- to 7-membered cycloalkyl group a —$(CH_2)_2$ group may be replaced by a —CO—NH group, a —$(CH_2)_3$ group may be replaced by a —NH—CO—NH or —CO—NH—CO group or a —$(CH_2)_4$ group may be replaced by a —NH—CO—NH—CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C1–3-alkyl group,

an aryl or heteroaryl group,

a hydroxy or C_{1-3}-alkoxy group,

an amino, C_{1-7}-alkylamino, di-(C_{1-7}-alkyl)-amino, phenylamino, N-phenyl-C_{1-3}-alkyl-amino, phenyl-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

an ω-hydroxy-C_{2-3}-alkyl-amino, N—(C_{1-3}-alkyl)-ω-hydroxy-C_{2-3}-alkyl-amino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino, di-(ω-(C_{1-3}-alkoxy)—C_{2-3}-alkyl)-amino or N-(dioxolan-2-yl)—C_{1-3}-alkyl-amino group,

a C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a C_{1-3}-alkylsulphonylamino, N—(C_{1-3}-alkyl)—C_{1-3}-alkylsulphonylamino, C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a hydroxycarbonyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-hydroxycarbonyl-C_{1-3}-alkyl-amino group,

a guanidino group wherein one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group,

a group of formula

$$—N(R_8)—CO—(CH_2)_n—R_9 \quad (II),$$

wherein

R_8 denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R_9 denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino, N—(C_{1-4}-alkyl)-phenylamino, benzylamino, N—(C_{1-4}-alkyl)-benzylamino or C_{1-4}-alkoxy group, a 4- to 7-membered cycloalkyleneimino group, whilst in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula

$$—N(R_{10})—(CH_2)_m—(CO)_o—R_{11} \quad (III),$$

wherein

R_{10} denotes a hydrogen atom, a C_{1-3}-alkyl group, a C_{1-3}-alkylcarbonyl, arylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, C_{1-3}-alkylsulphonyl, arylsulphonyl or phenyl-C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2, 3 or 4,

o denotes the number 1 or, if m denotes one of the numbers 2, 3 or 4, o may also denote the number 0 and

R_{11} denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino, N—(C_{1-4}-alkyl)-phenylamino, benzylamino, N—(C_{1-4}-alkyl)-benzylamino, C_{1-4}-alkoxy or C_{1-3}-alkoxy-C_{1-3}-alkoxy group, a di-(C_{1-4}-alkyl)-amino-C_{1-3}-alkylamino group optionally substituted in the 1 position by a C_{1-3}-alkyl group or a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl ring or in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group,

a C_{4-7}-cycloalkylamino, C_{4-7}-cycloalkyl-C_{1-3}-alkylamino or C_{4-7}-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond and wherein the abovementioned groups may each additionally be substituted at the amino-nitrogen atom by a C_{5-7}-cycloalkyl, C_{2-4}-alkenyl or C_{1-4}-alkyl group,

a 4- to 7-membered cycloalkyleneimino group, wherein

the cycloalkylene moiety may be fused to a phenyl group or to an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a nitro, C_{1-3}-alkyl, C_{1-3}-alkoxy or amino group, and/or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and/or

the methylene group in the 3 position of a 5-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy or C_{1-3}-alkoxy-C_{1-3}-alkyl group,

the methylene group in the 3 or 4 position of a 6- or 7-membered cycloalkyleneimino group may in each

case be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkoxy-C_{1-3}-alkyl, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkyl-amino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl-), —N(phenyl), —N(phenyl-C_{1-3}-alkyl-), —N(C_{1-3}-alkyl-carbonyl-), —N(C_{1-4}-hydroxy-carbonyl-), —N(C_{1-4}-alkoxy-carbonyl-), —N(benzoyl-) or —N(phenyl-C_{1-3}-alkyl-carbonyl-) group,

wherein a methylene group linked to an imino-nitrogen atom of the cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl group or in a 5- to 7-membered monocyclic cycloalkyleneimino group or a cycloalkyleneimino group fused to a phenyl group the two methylene groups linked to the imino-nitrogen atom may each be replaced by a carbonyl group,

or R_6 denotes a C_{1-4}-alkyl group which is substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

an N—(C_{1-3}-alkyl)—C_{2-4}-alkanoylamino group which is additionally substituted in the alkyl moiety by a carboxy or C_{1-3}-alkoxycarbonyl group,

a group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein

R_{12} denotes a hydrogen atom, a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group or a C_{1-3}-alkyl group terminally substituted by a phenyl, heteroaryl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, aminocarbonyl, C_{1-4}-alkylamino-carbonyl, di-(C_{1-4}-alkyl)-amino-carbonyl, C_{1-3}-alkyl-carbonyl, C_{1-3}-alkyl-sulphonylamino, N—(C_{1-3}-alkyl)—C_{1-3}-alkyl-sulphonylamino, C_{1-3}-alkyl-aminosulphonyl or di-(C_{1-3}-alkyl)-aminosulphonyl group and

p denotes one of the numbers 0, 1, 2 or 3 and

R_{13} assumes the meanings of the abovementioned group R_7, or, if p denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula

$$—N(R_{14})—(CH_2)_q—(CO)_r—R_{15} \quad (V),$$

wherein

R_{14} denotes a hydrogen atom, a C_{1-4}-alkyl group, a C_{1-3}-alkylcarbonyl, arylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, heteroarylcarbonyl, heteroaryl-C_{1-3}-alkylcarbonyl, C_{1-4}-alkylsulphonyl, arylsulphonyl, phenyl-C_{1-3}-alkylsulphonyl, heteroarylsulphonyl or heteroaryl-C_{1-3}-alkyl-sulphonyl group,

q denotes one of the numbers 1, 2, 3 or 4,

r denotes the number 1 or, if q is one of the numbers 2, 3 or 4, it may also denote the number 0 and

R_{15} assumes the meanings of the abovementioned group R_7,

a group of formula

$$—N(R_{16})—SO_2—R_{17} \quad (VI),$$

wherein

R_{16} denotes a hydrogen atom or a C_{1-4}-alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or N—(C_{1-3}-alkyl)-trifluoromethyl-carbonyl-amino group and

R_{17} denotes a C_{1-3}-alkyl group,

an amino group substituted by a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-carbonyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-sulphonyl group and a di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyl group,

or an N—(C_{1-3}-alkyl)—C_{1-5}-alkylsulphonylamino or N—(C_{1-3}-alkyl)-phenylsulphonylamino group wherein the alkyl moiety is additionally substituted by a cyano or carboxy group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R_6 may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-5}-alkyl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylamino-carbonyl, di-(C_{1-4}-alkyl)-amino-carbonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl, di-(C_{1-3}-alkyl)-aminosulphonyl, C_{1-3}-alkyl-sulphonylamino, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group, and

R_5 denotes a hydrogen atom or a C_{1-3}-alkyl group,

wherein by an aryl group is meant a phenyl or naphthyl group optionally mono- or disubstituted by a fluorine, chlorine, bromine or iodine atom, by a cyano, trifluoromethyl, nitro, carboxy, aminocarbonyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group and

by a heteroaryl group is meant a monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C_{1-3}-alkyl group in the carbon skeleton, wherein

the 6-membered heteroaryl group contains one, two or three nitrogen atoms and

the 5-membered heteroaryl group contains an imino group optionally substituted by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group, an oxygen or sulphur atom or

an imino group optionally substituted by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group or an oxygen or sulphur atom and additionally a nitrogen atom or

an imino group optionally substituted by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group and two nitrogen atoms,

and moreover a phenyl ring may be fused to the abovementioned monocyclic heterocyclic groups via two adjacent carbon atoms and the bonding takes place via a nitrogen atom or via a carbon atom of the heterocyclic moiety or a fused phenyl ring,

some or all of the hydrogen atoms in the abovementioned alkyl and alkoxy groups or in the alkyl moieties contained in the above-defined groups of formula I may be replaced by fluorine atoms,

and wherein any carboxy group contained in the abovementioned groups may be replaced by a tert.butoxycarbonyl precursor group,

and wherein a hydrogen atom bound to a nitrogen atom may each be replaced by hydroxyl, benzoyl, pyridinoyl, formyl, acetyl, propionyl, butanoyl, pentanoyl, hexanoyl, allyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl,

hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, hexadecyloxycarbonyl, benzyloxycarbonyl, phenylethoxycarbonyl, phenylpropoxycarbonyl, C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or an R_eCO—O—(R_fCR_g)—O—CO group wherein

R_e denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_f denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C_{1-3}-alkyl or R_eCO—O—(R_fCR_g)—O group wherein R_e to R_g are as hereinbefore defined,

or wherein an amino nitrogen may form part of a phthalimido group,

or a tautomer or salt thereof.

2. A compound of the formula I according to claim **1**, wherein:

R_1 and R_3 are as defined in claim **1**,

X denotes an oxygen atom,

R_2 denotes a carboxy group, a straight-chain or branched C_{1-6}-alkoxy-carbonyl group, a C_{5-7}-cycloalkoxycarbonyl or a phenoxycarbonyl group,

a straight-chain or branched C_{1-3}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, heteroaryl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a straight-chain or branched C_{2-3}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a chlorine atom, by a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group,

R_4 denotes a C_{3-7}-cycloalkyl group,

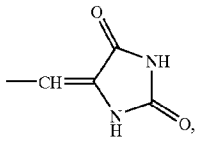
whilst the methylene group in the 4 position of a 6 or 7-membered cycloalkyl group may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group,

or a phenyl group substituted by the group R_6, which may additionally be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C_{1-3}-alkyl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, amino, acetylamino, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, nitro or cyano groups, wherein the substituents may be identical or different and wherein

R_6 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom,

a cyano, nitro, amino, C_{1-5}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl, phenyl, tetrazolyl or heteroaryl group,

the group of formula



wherein a hydrogen atom bound to the nitrogen atom may be replaced by a C_{1-3}-alkyl group,

a C_{1-3}-alkoxy group, an amino-C_{2-3}-alkoxy, C_{1-3}-alkylamino-C_{2-3}-alkoxy, di-(C_{1-3}-alkyl)-amino-C_{2-3}-alkoxy, phenyl-C_{1-3}-alkylamino-C_{2-3}-alkoxy, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino-C_{2-3}-alkoxy, pyrrolidino-C_{2-3}-alkoxy, piperidino-C_{2-3}-alkoxy or C_{1-3}-alkylmercapto group,

a carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, phenyl-C_{1-3}-alkylamino-carbonyl or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino-carbonyl group,

a C_{3-7}-cycloalkyl-carbonyl group,

wherein the methylene group in the 4 position of the 6- or 7-membered cycloalkyl moiety may be replaced by an —NH or —N(C_{1-3}-alkyl) group,

a 4- to 7-membered cycloalkyleneimino group, wherein

a methylene group linked to the imino group may be replaced by a carbonyl or sulphonyl group or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH or —N(C_{1-3}-alkyl) group,

a C_{1-4}-alkyl group terminally substituted by the group R_7, wherein

R_7 denotes a C_{5-7}-cycloalkyl group,

whilst the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an —NH or —N(C_{1-3}-alkyl) group or

in a 5- to 7-membered cycloalkyl group a —$(CH_2)_2$ group may be replaced by a —CO—NH group, a —$(CH_2)_3$ group may be replaced by a —NH—CO—NH— or a —$(CH_2)_4$ group may be replaced by a —NH—CO—NH—CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl group,

a phenyl or heteroaryl group,

a hydroxy or C_{1-3}-alkoxy group,

an amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)-amino, phenylamino, N-phenyl-C_{1-3}-alkyl-amino, phenyl-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino or di-(phenyl-C_{1-3}-alkyl)-amino group,

a ω-hydroxy-C_{2-3}-alkyl-amino, N—(C_{1-3}-alkyl)ω-hydroxy-C_{2-3}-alkyl-amino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino, di-(ω-(C_{1-3}-alkoxy)—C_{2-3}-alkyl)-amino or N—(dioxolan-2-yl)—C_{1-3}-alkyl-amino group,

a C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a C_{1-3}-alkylsulphonylamino, N—(C_{1-3}-alkyl)—C_{1-3}-alkylsulphonylamino, C_{1-3}-alkylsulphonylamino-C_{2-3}-

alkyl-amino or C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a hydroxycarbonyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-hydroxycarbonyl-C_{1-3}-alkyl-amino group

a guanidino group wherein a hydrogen atom may be replaced by a C_{1-3}-alkyl group,

a group of formula

$$—N(R_8)—CO—(CH_2)_n-R_9 \quad (II),$$

wherein

R_8 denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R_9 denotes an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenylamino, benzylamino or C_{1-4}-alkoxy group, a 5- to 7-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group, or, if n denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula

$$—N(R_{10})—(CH_2)_m—(CO)_o-R_{11} \quad (III),$$

wherein

R_{10} denotes a hydrogen atom, a C_{1-3}-alkyl group, a C_{1-3}-alkylcarbonyl or C_{1-3}-alkylsulphonyl group,

m denotes one of the numbers 1, 2 or 3,

o denotes the number 1 or, if m is one of the numbers 2 or 3, o may also denote the number 0 and

R_{11} denotes an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-4}-alkoxy or C_{1-3}-alkoxy-C_{1-3}-alkoxy group or a 5- to 7-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(C_{1-3}-alkyl-carbonyl) or —N(benzoyl) group,

a C_{4-7}-Cycloalkylamino or C_{4-7}-cycloalkenylamino group wherein position 1 of the ring is not involved in the double bond,

a 4- to 7-membered cycloalkyleneimino group, wherein the cycloalkylene moiety may be fused to a phenyl group or

one or two hydrogen atoms may each be replaced by a C_{1-3}-alkyl group and/or

the methylene group in position 3 of the pyrrolidino group may be substituted by a hydroxy or C_{1-3}-alkoxy group,

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(phenyl), —N(phenyl-C_{1-3}-alkyl), —N(C_{1-3}-alkyl-carbonyl), —N(C_{1-4}-alkoxycarbonyl), —N(benzoyl) or —N(phenyl-C_{1-3}-alkyl-carbonyl) group,

wherein a methylene group linked to an imino-nitrogen atom of the cycloalkyleneimino group may be replaced by a carbonyl or sulphonyl group or in a 5- to 6-membered monocyclic cycloalkyleneimino group or a cycloalkyleneimino group fused to a phenyl group the two methylene groups linked to the imino-nitrogen atom may each be replaced by a carbonyl group,

or R_6 denotes a C_{1-4}-alkyl group which is terminally substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group or by a 4- to 7-membered cycloalkyleneiminocarbonyl group,

a group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein

R_{12} denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl group and

p denotes one of the numbers 0, 1, 2 or 3 and

R_{13} assumes the meanings of the abovementioned group R_7, or, if p denotes one of the numbers 1, 2 or 3, it may also denote a hydrogen atom,

a group of formula

$$—N(R_{14})—(CH_2)_q—(CO)_r—R_{15} \quad (V),$$

wherein

R_{14} denotes a hydrogen atom, a C_{1-4}-alkyl group, a C_{1-3}-alkylcarbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, heteroarylcarbonyl, heteroaryl-C_{1-3}-alkylcarbonyl, C_{1-4}-alkylsulphonyl, phenylsulphonyl, phenyl-C_{1-3}-alkylsulphonyl-heteroarylsulphonyl or heteroaryl-C_{1-3}-alkyl-sulphonyl group,

q denotes one of the numbers 1, 2, 3 or 4,

r denotes the number 1 or, if q is one of the numbers 2, 3 or 4, it may also denote the number 0 and

R_{15} assumes the meanings of the abovementioned group R_7,

a group of formula

$$—N(R_{16})—SO_2—R_{17} \quad (VI),$$

wherein

R_{16} denotes a hydrogen atom or a C_{1-4}-alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or N—(C_{1-3}-alkyl)-trifluoromethyl-carbonyl-amino group and

R_{17} denotes a C_{1-3}-alkyl group,

an amino group substituted by a di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-carbonyl or di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-sulphonyl group and a di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyl group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R_6 may be mono- or disubstituted by fluorine, chlorine or bromine atoms, by C_{1-3}-alkyl, trifluoromethyl, hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl, nitro or cyano groups, wherein the substituents may be identical or different, or two adjacent hydrogen atoms of the phenyl groups may be replaced by a methylenedioxy group, and

R_5 denotes a hydrogen atom or a C_{1-3}-alkyl group,

whilst by a heteroaryl group as mentioned above is meant a pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl,

pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, pyrazolyl, imidazolyl or triazolyl group optionally substituted in the carbon skeleton by a C_{1-3}-alkyl group wherein a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group and wherein the 5-membered heteroaryl groups containing at least one imino group are bound via a carbon or nitrogen atom,

a hydrogen atom bound to a nitrogen atom in the above-mentioned groups may be replaced by hydroxyl, benzoyl, pyridinoyl, formyl, acetyl, propionyl, butanoyl, pentanoyl, hexanoyl, allyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, hexadecyloxycarbonyl, benzyloxycarbonyl, phenylethoxycarbonyl, phenylpropoxycarbonyl, C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or an $R_eCO—O—(R_fCR_g)—O—CO$ group wherein

R_e denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_f denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C_{1-3}-alkyl or $R_eCO—O—(R_fCR_g)—O$ group wherein R_e to R_g are as hereinbefore defined,

or wherein an amino nitrogen may form part of a phthalimido group,

and wherein any carboxy group contained in the above-mentioned groups may be replaced by a tert.butoxycarbonyl precursor group,

and wherein some or all of the hydrogen atoms in the abovementioned alkyl and alkoxy groups or in the alkyl moieties contained in the above-defined groups of formula I may be replaced by fluorine atoms,

or a tautomer or salt thereof.

3. A compound of the formula I according to claim **1**, wherein:

X denotes an oxygen atom,

R_1 denotes a hydrogen atom,

R_2 denotes a carboxy group, a straight-chain or branched C_{1-4}-alkoxycarbonyl group or a phenoxycarbonyl group,

a straight-chain or branched C_{1-3}-alkoxy-carbonyl group, which is terminally substituted in the alkyl moiety by a phenyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a straight-chain or branched C_{2-3}-alkoxy-carbonyl group which is terminally substituted in the alkyl moiety by a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an aminocarbonyl or methylaminocarbonyl group, an ethylaminocarbonyl group optionally substituted in the 2 position of the ethyl group by a hydroxy or C_{1-3}-alkoxy group or, if R_4 does not denote an aminosulphonyl-phenyl or N—(C_{1-5}-alkyl)—C_{1-3}-alkylaminocarbonyl-phenyl group, it may also denote a di-(C_{1-2}-alkyl)-aminocarbonyl group,

R_3 denotes a C_{1-4}-alkyl group or a phenyl group which may be substituted by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl, hydroxy or C_{1-3}-alkoxy group,

R_4 denotes a C_{5-6}-cycloalkyl group,

wherein the methylene group in position 4 of the cyclohexyl group may be substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group or replaced by an —NH or —N(C_{1-3}-alkyl) group,

a phenyl group, a phenyl group disubstituted by C_{1-3}-alkyl, C_{1-3}-alkoxy or nitro groups, wherein the substituents may be identical or different, or

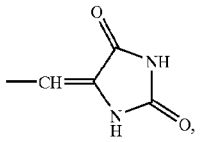
a phenyl group substituted by the group R_6, which may additionally be substituted by a fluorine, chlorine or bromine atom or by an amino or nitro group, wherein

R_6 denotes a fluorine, chlorine or bromine atom,

a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro, amino or C_{5-6}-cycloalkyl group,

a pyrrolyl, pyrazolyl, imidazolyl, triazolyl or tetrazolyl group bound via a carbon atom, wherein the abovementioned heteroaromatic groups in the carbon skeleton may be substituted by a C_{1-3}-alkyl group or a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group,

the group of formula



a carboxy, C_{1-4}-alkoxycarbonyl, phenyl-C_{1-3}-alkylaminocarbonyl or C_{5-7}-cycloalkyl-carbonyl group,

a 5 or 6-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an oxygen or sulphur atom, by an —NH or —N(C_{1-3}-alkyl) group,

an unbranched C_{1-3}-alkyl group terminally substituted by the group R_7, wherein

R_7 denotes a C_{5-7}-cycloalkyl group,

wherein in a 5 or 6-membered cycloalkyl group a $—(CH_2)_2$ group may be replaced by a —CO—NH group, a $—CH_2)_3$ group may be replaced by an —(NH—CO—NH— or a $—(CH_2)_4$ group may be replaced by an —NH—CO—NH—CO group, whilst in each case a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl group,

a phenyl or pyridinyl group or a pyrrolyl, pyrazolyl, imidazolyl or triazolyl group bound via a carbon or nitrogen atom, wherein the abovementioned heteroaromatic groups in the carbon skeleton may be substituted by a C_{1-3}-alkyl group or a hydrogen atom bound to a nitrogen atom may be replaced by a C_{1-3}-alkyl group,

a hydroxy or C_{1-3}-alkoxy group,

an amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)-amino, phenylamino, N-phenyl-C_{1-3}-alkylamino, phenyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group,

a ω-hydroxy-C_{2-3}-alkyl-amino, N—(C_{1-3}-alkyl)-ω-hydroxy-C_{2-3}-alkylamino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino or di-(ω-(C_{1-3}-alkoxy)—C_{2-3}-alkyl)-amino group,

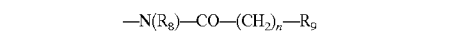
a C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-amino or C_{1-3}-alkylcarbonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a C_{1-3}-alkylsulphonylamino, N—(C_{1-3}-alkyl)—C_{1-3}-alkylsulphonylamino, C_{1-3}-alkylsulphonylamino-C_{2-3}-alkylamino or C_{1-3}-alkylsulphonylamino-C_{2-3}-alkyl-N—(C_{1-3}-alkyl)-amino group,

a hydroxycarbonyl-C_{1-3}-alkylamino or N—(C_{1-3}-alkyl)-hydroxycarbonyl-C_{1-3}-alkyl-amino group,

a guanidino group wherein a hydrogen atom may be replaced by a C_{1-3}-alkyl group,

a group of formula



$$—N(R_8)—CO—(CH_2)_n—R_9 \quad (II),$$

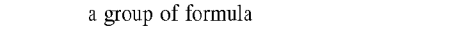
wherein

R_8 denotes a hydrogen atom or a C_{1-3}-alkyl group,

n denotes one of the numbers 0, 1, 2 or 3 and

R_9 denotes an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino or C_{1-4}-alkoxy group, a 5- or 6-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an —NH, —N(C_{1-3}-alkyl) or —N(C_{1-3}-alkyl-carbonyl) group, or, if n denotes one of the numbers 1, 2 or 3, R_9 may also denote a hydrogen atom,

a group of formula



$$—N(R_{10})—(CH_2)_m—(CO)_o—R_{11} \quad (III),$$

wherein

R_{10} denotes a hydrogen atom or a C_{1-3}-alkyl group,

m denotes one of the numbers 1, 2 or 3,

o denotes the number 1 or, if m is one of the numbers 2 or 3, o may also denote the number 0 and

R_{11} denotes an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-4}-alkoxy or methoxy-C_{1-3}-alkoxy group or a 5- or 6-membered cycloalkyleneimino group, wherein the methylene group in position 4 of the piperidino group may be replaced by an —NH, —N(C_{1-3}-alkyl) or —N(C_{1-3}-alkyl-carbonyl) group,

an azetidino, pyrrolidino, piperidino, 2,6-dimethyl-piperidino, 3,5-dimethyl-piperidino or azepino group, wherein

the methylene group in position 3 of the pyrrolidino group may be substituted by a hydroxy group,

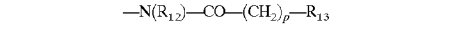
the methylene group in position 4 of the piperidino group may be substituted by a hydroxy, hydroxy-C_{1-3}-alkyl or C_{1-3}-alkoxy group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, —NH, —N(C_{1-3}-alkyl), —N(C_{1-3}-alkyl-carbonyl), —N(benzoyl) or —N(phenyl-C_{1-3}-alkyl-carbonyl) group,

wherein a methylene group linked to an imino-nitrogen atom of the pyrrolidino, piperidino or piperazino group may be replaced by a carbonyl group,

or R_6 denotes a straight-chain C_{1-3}-alkyl group which is terminally substituted by a carboxy or C_{1-3}-alkoxy-carbonyl group,

a group of formula



$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein

R_{12} denotes a hydrogen atom, a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group,

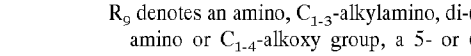
p denotes one of the numbers 0, 1 or 2 and

R_{13} denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, benzylamino, N—(C_{1-3}-alkyl)-benzylamino, C_{1-3}-alkoxy-C_{1-3}-alkylamino, N—(C_{1-3}-alkyl)-C_{1-3}-alkoxy-C_{1-3}-alkylamino, di-(2-methoxy-ethyl)-amino, di-(ω-hydroxy-C_{2-3}-alkyl)-amino or aminocarbonyl-methyl-N-(methyl)-amino group,

a pyrrolyl, pyrazolyl or imidazolyl group bound via a nitrogen atom and optionally substituted by a C_{1-3}-alkyl group,

a pyrrolidino, piperidino, morpholino, thiomorpholino or a piperazino group optionally substituted in the 4 position by a C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl or C_{1-4}-alkoxycarbonyl group or, if n denotes the number 1 or 2, it may also denote a hydrogen atom,

a group of formula



$$—N(R_{14})—CH_2)_q—(CO)_r—R_{15} \quad (V),$$

wherein

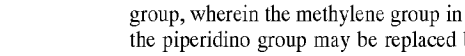
R_{14} denotes a hydrogen atom, a C_{1-4}-alkyl, C_{1-3}-alkyl-carbonyl, phenylcarbonyl, phenyl-C_{1-3}-alkylcarbonyl, furyl-carbonyl, pyridinyl-carbonyl, furyl-C_{1-3}-alkylcarbonyl, pyridinyl-C_{1-3}-alkylcarbonyl, C_{1-4}-alkylsulphonyl, phenylsulphonyl or phenyl-C_{1-3}-alkylsulphonyl group,

q denotes one of the numbers 1, 2 or 3,

r denotes the number 1 or, if q is one of the numbers 2 or 3, it may also denote the number 0 and

R_{15} denotes an amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, phenylamino, N—(C_{1-4}-alkyl)-phenylamino, benzylamino or N—(C_{1-4}-alkyl)-benzylamino group,

or a group of formula



$$—N(R_{16})—SO_2—R_{17} \quad (VI),$$

wherein

R_{16} denotes a hydrogen atom or a C_{1-3}-alkyl group optionally terminally substituted by a cyano, trifluoromethyl-carbonylamino or N—(C_{1-3}-alkyl)-trifluoromethyl-carbonyl-amino group and

R_{17} denotes a C_{1-3}-alkyl group,

wherein all the single-bonded or fused phenyl groups contained in the groups mentioned under R_6 may be substituted by a fluorine, chlorine or bromine atom, by a methyl, trifluoromethyl, methoxy, nitro or cyano group and

R_5 denotes a hydrogen atom,

wherein a hydrogen atom bound to a nitrogen atom in the abovementioned groups may be replaced by an acetyl or tert.butoxycarbonyl group,

the carboxy groups contained in the abovementioned groups may also be present in the form of the tert.butoxycarbonyl precursor group,

or a tautomer or salt thereof.

4. A compound of the formula I according to claim **1**, wherein:

X denotes an oxygen atom,

R_1 and R_5 each denote a hydrogen atom,

R_2 denotes a methoxycarbonyl, ethoxycarbonyl or aminocarbonyl group,

R_3 denotes a phenyl group and

R_4 denotes a phenyl group monosubstituted by the group R_6, wherein

R_6 denotes an N-methyl-imidazol-2-yl group,

an unbranched C_{1-3}-alkyl group which is terminally substituted by a C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, piperidino or 2,6-dimethyl-piperidino group,

a group of formula

$$—N(R_{12})—CO—(CH_2)_p—R_{13} \quad (IV),$$

wherein

R_{12} denotes a C_{1-3}-alkyl group,

p denotes one of the numbers 1 or 2 and

R_{13} denotes a di-(C_{1-3}-alkyl)-amino group,

or a group of formula

$$—N(R_{14})—(CH_2)_q—(CO)_r—R_{15} \quad (V),$$

wherein

R_{14} denotes a C_{1-3}-alkyl-carbonyl or C_{1-3}-alkylsulphonyl group,

q denotes one of the numbers 1, 2 or 3,

r denotes the number 1 or, if q is one of the numbers 2 or 3, r may also denote the number 0 and

R_{15} denotes a di-(C_{1-3}-alkyl)-amino group,

or a tautomer or salt thereof.

5. A compound selected from the group consisting of:

(a) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(b) 3-Z-[(1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-carbamoyl-2-indolinone,

(c) 3-Z-[1-(4-(piperidin-1-yl-methyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(d) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(e) 3-Z-[1-(4-((2,6-dimethyl-piperidin-1-yl)-methyl)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(f) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(g) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(h) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-ethoxycarbonyl-2-indolinone,

(i) 3-Z-[1-(4-(dimethylaminomethyl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(j) 3-Z-[1-(4-(N-acetyl-N-dimethylaminocarbonylmethyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(k) 3-Z-[1-(4-ethylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(l) 3-Z-[1-(4-(1-methyl-imidazol-2-yl)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(m) 3-Z-[1-(4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(n) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(o) 3-Z-[1-(4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(p) 3-Z-[1-(4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(q) 3-Z-[1-(4-(N-((2-dimethylamino-ethyl)-carbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(r) 3-Z-[1-(4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

(s) 3-Z-[1-(4-methylaminomethyl-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone and

(t) 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone,

or a tautomer or salt thereof.

6. A physiologically acceptable salt of a compound according to claims **1**, **2**, **3**, **4** or **5**.

7. A pharmaceutical composition containing a compound according to claims **1**, **2**, **3** or **4**, or a physiologically acceptable salt thereof in accordance with claim **5**, together with a pharmaceutically acceptable carrier.

8. 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone or a pharmaceutically acceptable salt thereof.

* * * * *

EXHIBIT 2

Patent eBusiness
- Electronic Filing
- Patent Application Information (PAIR)
- Patent Ownership
- Fees
- Supplemental Resources & Support

Patent Information
Patent Guidance and General Info
- Codes, Rules & Manuals
- Employee & Office Directories
- Resources & Public Notices

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- Search Biological Sequences
- Copies, Products & Services

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Reports

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09/678,682 SUBSTITUTED INDOLINES WHICH INHIBIT RECEPTOR TYROSINE KINASES 05-1275

Select New Case | Application Data | Transaction History | Image File Wrapper | Patent Term Adjustments | Continuity Data | Foreign Priority | Fees | Published Documents | Address & Attorney/Agent | Display References

Patent Term Adjustment

Filing or 371(c) Date:	10-03-2000	Overlapping Days Between {A and B} or {A and C}:	0
Issue Date of Patent:	07-13-2004	Non-Overlapping USPTO Delays:	201
A Delays:	201	PTO Manual Adjustments:	0
B Delays:	0	Applicant Delays:	133
C Delays:	0	Total PTA Adjustments:	68

Patent Term Adjustment History Explanation Of Calculations

Number	Date	Contents Description	PTO(Days)	APPL (Days)	Start
56	07-13-2004	Patent Issue Date Used in PTA Calculation			0
55	06-14-2004	Receipt into Pubs			0
54	04-12-2004	Issue Fee Payment Verified			0
53	05-29-2004	Application Is Considered Ready for Issue			0
52	04-12-2004	Issue Fee Payment Verified			0
51	04-12-2004	Issue Fee Payment Received			0
50	04-05-2004	Workflow - File Sent to Contractor			0
49	03-10-2004	Mail Notice of Allowance			0
48	03-08-2004	Issue Revision Completed			0
47	03-08-2004	Notice of Allowance Data Verification Completed			0
46	03-08-2004	Case Docketed to Examiner in GAU			0
45	03-08-2004	Allowability Notice			0
44	02-13-2004	IFW Amended case processing Complete			0
43	02-13-2004	Date Forwarded to Examiner			0
42	12-08-2003	Amendment Submitted/Entered with Filing of CPA/RCE			0
41	02-13-2004	Date Forwarded to Examiner			0
40	12-08-2003	Request for Continued Examination (RCE)			0
39	02-13-2004	Disposal for a RCE / CPA / R129			0
38	12-08-2003	Request for Extension of Time - Granted			0
37	12-08-2003	Workflow - Request for RCE - Begin			0
36	06-13-2003	Mail Final Rejection (PTOL - 326)			0
35	06-13-2003	Final Rejection			0
34	06-06-2003	Date Forwarded to Examiner			0
33	05-16-2003	Supplemental Response		3	31
32	05-24-2003	Date Forwarded to Examiner			0
31	05-13-2003	Response after Non-Final Action		84	29
30	05-13-2003	Request for Extension of Time - Granted			0
29	11-18-2002	Mail Non-Final Rejection	115		25
28	11-18-2002	Non-Final Rejection			0
27	10-31-2002	Case Docketed to Examiner in GAU			0
26	10-30-2002	Date Forwarded to Examiner			0
25	03-26-2002	Response to Election / Restriction Filed			0
24	10-31-2002	Mail Notice of Rescinded Abandonment			0
23	10-28-2002	Notice of Rescinded Abandonment in TCs			0
22	10-07-2002	Mail Examiner Interview Summary (PTOL - 413)			0
21	10-07-2002	Mail Abandonment for Failure to Respond to Office Action			0
20	10-07-2002	Aband. for Failure to Respond to O. A.			0
19	09-30-2002	Examiner Interview Summary Record (PTOL - 413)			0
18	02-27-2002	Mail Restriction Requirement	86		-1
17	02-27-2002	Restriction/Election Requirement			0
16	02-20-2002	Case Docketed to Examiner in GAU			0
15	02-20-2002	Case Docketed to Examiner in GAU			0
14	02-20-2002	File Marked Found			0
13	01-18-2002	File Marked Lost			0
12	11-15-2001	Case Docketed to Examiner in GAU			0
11	02-26-2001	Case Docketed to Examiner in GAU			0

10	07-25-2001	Case Docketed to Examiner in GAU		0
9	02-26-2001	Information Disclosure Statement (IDS) Filed		0
8	04-21-2001	Case Docketed to Examiner in GAU		0
7	04-18-2001	Application Dispatched from OIPE		0
6	04-16-2001	Application Is Now Complete		0
5	04-16-2001	Application Is Now Complete	46	4
4	12-01-2000	Notice Mailed--Application Incomplete--Filing Date Assigned		0
3	11-30-2000	Correspondence Address Change		0
2	11-03-2000	IFW Scan & PACR Auto Security Review		0
1	10-03-2000	Initial Exam Team nn		0

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- *Call the Patent Electronic Business Center at (866) 217-9197 (toll free) or e-mail EBC@uspto.gov for specific questions about Patent Application Information Retrieval (PAIR).*
- *Send general questions about USPTO programs to the USPTO Contact Center (UCC) .*
- *If you experience technical difficulties or problems with this application, please report them via e-mail to Electronic Business Support or call 1 800-786-9199.*

EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
Alexandria Division

EXELIXIS, INC.,	)	
Plaintiff,	)	
	)	
v.	)	**Case No. 1:12cv96**
	)	
HON. DAVID J. KAPPOS, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office,	)	
Defendant.	)	

MEMORANDUM OPINION

In the 1990's, Congress twice significantly altered the patent law landscape. First, in 1994, Congress enacted the Uruguay Round Agreements Act,[1] which (i) required the term of a patent to be measured from the date of application, (ii) extended a patent term from 17 to 20 years, and (iii) created patent term adjustment ("PTA"), extending the length of a patent term in the event that certain delays occurred in the processing of the application. Second, in 1999, Congress again altered the patent landscape by enacting the American Inventors Protection Act of 1999 ("AIPA"),[2] which significantly amended the PTA provisions and provided for a Request for Continued Examination ("RCE"), which permits an applicant to request additional examination of the patent application. Predictably, these alterations in the patent law landscape spawned substantial litigation, of which this case is a recent example.

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[1] Pub. L. No. 103–465, Dec. 8, 1994, 108 Stat. 4809 (codified as amended in scattered sections of 35 U.S.C.).

[2] Pub. L. No. 106–113, 113 Stat. 1536 (codified as amended in scattered sections of 35 U.S.C.).

Presented here is the following, as yet unresolved, question concerning the application of AIPA's PTA provision:

> Whether 35 § 154(b)(1)(B) requires that an applicant's PTA be reduced by the time attributable to an RCE, where, as here, the RCE is filed after the expiration of AIPA's guaranteed three year period.

For the reasons that follow, § 154's plain language neither addresses nor requires that an applicant's PTA be reduced by the time required to process an RCE that is filed after the expiration of the three year period.[3]

I.

Exelixis, Inc. ("Exelixis"), a Delaware corporation with its principal place of business in San Francisco, California, is the owner of United States Patent No. 7,989,622 ("the '622 patent"). This patent—entitled "Phosphatidylinositol 3-Kinase Inhibitors and Methods of their Use"— covers certain molecules that inhibit an enzyme associated with certain cancers that may be useful for the treatment and prevention of those cancers.

The administrative record reflects the various events that occurred in the course of the prosecution and examination of the application that led to the issuance of the patent. Only a few of these events—those pertinent to the PTA calculation and hence to the question presented—merit mention here.

First, the record reflects that the application for the '622 patent[4] was filed on January 15, 2008. The record shows that the next event of PTA significance occurred on February 22, 2010,

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[3] Exelixis points out that if the question presented were decided to the contrary, it would be necessary to resolve a second question, namely whether the period of time between the date of the Notice of Allowance and the date of the patent issuance is properly included as "time consumed by continuing examination" under § 154(b)(1)(B)(i).

[4] This application was a national stage application of a Patent Cooperation Treaty application. The Patent Cooperation Treaty is "an international agreement allowing inventors to streamline

when the United States Patent and Trademark Office ("PTO") issued a "Restriction and/or Election Requirement," its first notice pursuant to 35 U.S.C. § 132. This filing came approximately 25 months after the application was filed. The timing of this PTO filing is important to the PTA calculation inasmuch as § 154(b)(1)(A) requires the PTO to provide at least one § 132 notice (or alternatively, a notice of allowance) not later than 14 months after the application is filed, and to the extent the § 132 misses this 14 month deadline, the applicant receives a day for day credit toward the PTA.

The next event with PTA significance occurred, as the record reflects, on March 9, 2011, approximately 38 months after the application filing date, when the PTO issued a Final Rejection of the application. Barely a month later, Exelixis, on April 11, 2011, filed the RCE at issue here. This RCE modified and supplemented the application as follows: (i) claims 1–12, 14, 15, and 17–33 were cancelled, (ii) claims 13 and 16 were amended, (iii) claims 34–38 were added, and (iv) additional support was provided for the amended and added claims.

Thereafter, the PTO, with commendable, if, with respect to this application, uncharacteristic alacrity, responded less than three weeks later by mailing to Exelixis a "Notice of Allowance & Fees Due" with respect to the application. This Notice advised Exelixis (i) that "prosecution on the merits has closed," (ii) that the application "is allowed for issuance as a patent," and (iii) that the PTA for the '622 patent was calculated as 283 days, meaning that the '622 patent term would extend 20 years plus 283 days from the date of the patent application.

The record next shows that on April 28, 2011, Exelixis paid the issue fee, but then for reasons not disclosed in the record, the PTO did not mail the "Issue Notification" to Exelixis

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the process of obtaining patent rights across multiple member nations." *Helfgott & Karas, P.C. v. Dickenson*, 209 F.3d 1328, 1330 (Fed. Cir. 2000).

until July 17, 2011. The '622 patent issued thereafter on August 2, 2011. The Issue Notification included the PTO's final PTA calculation for the patent,[5] totaling 368 days, consisting of (i) 344 days for PTA attributable to the PTO's failure to file a § 132 notification within 14 months of the patent application date, as required by § 154(b)(1)(A) ("A delay"), (ii) 85 days of PTA attributable to the PTO for the failure of a patent to issue within 3 years of the application date, as required by § 154(b)(1)(B) ("B delay"), (iii) 0 days of PTA pursuant to § 154(b)(1)(C) ("C delay"), and (iv) a 61 day PTA reduction attributable to Exelixis' delay pursuant to § 154(b)(2)(C) ("C reduction").

Exelixis does not dispute the PTO's calculation of A delay, C delay, or C reduction; instead, the parties' dispute focuses sharply on the PTO's B delay calculation. The PTO contends that the 85 days of B delay is arrived at by subtracting the number of days attributable to the RCE, 114 days (April 11, 2011 to August 2, 2011), from 199 days (the number of days from the expiration of the three year period—January 15, 2008 to January 15, 2011—to the issuance of the patent on August 2, 2011). Exelixis disagrees with the PTO's decision to reduce the PTA by the RCE and argues instead that the proper B delay calculation is 199 days, the number of days between the end of the § 154(b)(1)(B) guaranteed three year period (January 15, 2011) and the issuance of the patent (August 2, 2011). The following time line illustrates the '622 patent's path to issuance and the parties' competing B delay calculations:

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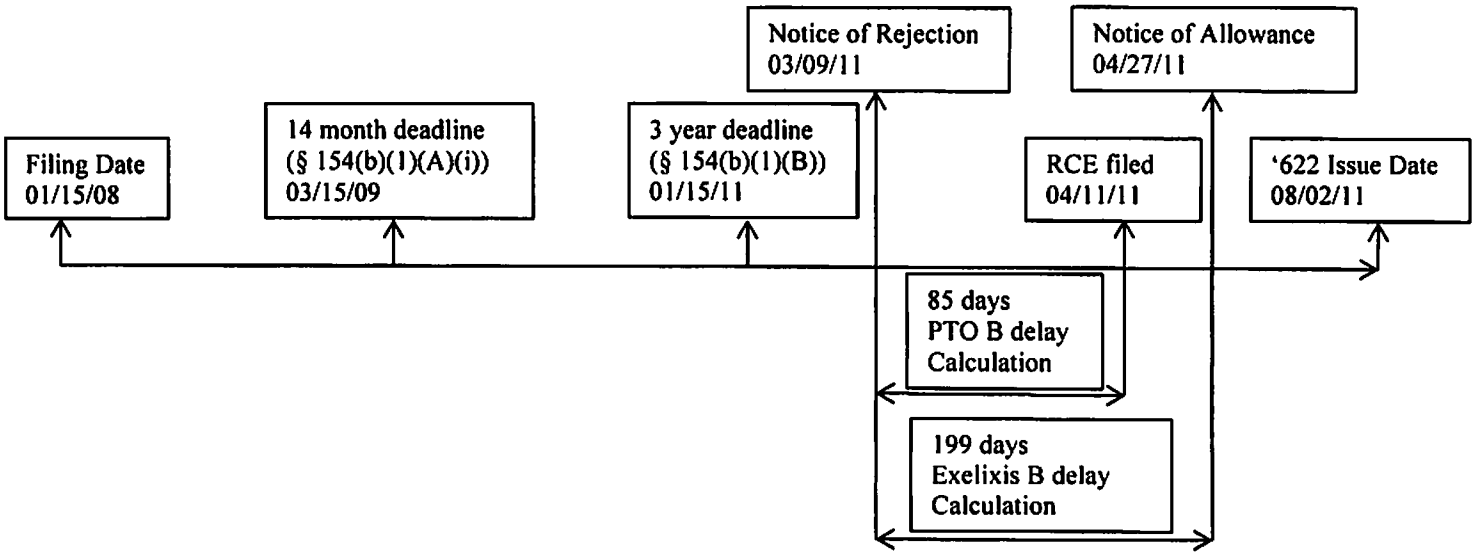
[5] The difference between the April 27, 2011 PTA calculation and the final PTA calculation reflects the addition of the B delay PTA.



As the timeline shows, the PTO's notice of rejection, Exelixis' RCE, the PTO's notice of allowance, and the issuance of the patent all occurred after the expiration of the three year period that commenced on the application filing date. And as the timeline also makes clear, the question that divides the parties on these facts is whether § 154(b)(1)(B) requires that, or even addresses whether, any PTA be reduced by time attributable to an RCE where, as here, the RCE is filed after the expiration of the three year guarantee period specified in that statute.

II.

Resolution of this question is informed by a brief overview of AIPA's PTA provisions. The starting point in this overview is to note that Congress, in 1994, in order to implement international agreements, amended the patent laws to extend the length of a patent term to 20 years, measured from the date of the patent application.[6] Prior to this amendment, a patent term was 17 years, measured not from the application date, but from the date of the patent issuance. Recognizing that the examination and prosecution phase might result in delays in the issuance of

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[6] Uruguay Round Agreements Act, Pub. L. No. 103–465, Dec. 8, 1994, 108 Stat. 4809 (codified as amended in scattered sections of 35 U.S.C.).

a patent, Congress in the 1994 amendment provided for adjusting the patent term to account for delays that might occur owing to "interference delay," "secrecy orders," or "appellate review."[7] Then, in 1999, Congress again amended these provisions to add the PTA provisions now found in § 154(b).[8] Taken as a whole, the clear goal and purpose of these provisions is to provide a successful applicant with a patent that can be enforced against putative infringers for approximately 17 years—20 years from the date of application less the three years for prosecution and examination—and to reach this goal by providing applicants with day for day patent term extensions for delays attributable to the PTO and day for day reductions of the patent term extension for delays attributable to an applicant's failure to act with alacrity in certain circumstances.

A. The Patent Application Process

In order to patent an invention, a person must apply to the PTO for a patent. 35 U.S.C. § 111. A PTO patent examiner then determines whether the "applicant is entitled to a patent under the law," and, if so, the PTO issues a patent. 35 U.S.C. § 131. If the patent examiner makes a contrary finding, then the PTO will issue a notice of rejection that puts forth "the reasons for such rejection." 35 U.S.C. § 132(a). If the applicant receives a rejection notice, the applicant may continue to pursue the issuance of the patent as is, or may make an amendment to the patent application. On the second, or any subsequent, examination of the patent application, the patent examiner may determine that the rejection is final. 37 C.F.R. § 1.113. The applicant's options

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[7] *Id.*

[8] AIPA, Pub. L. No. 106–113, 113 Stat. 1536 (codified as amended in scattered sections of 35 U.S.C.). The portion of the AIPA that altered the PTA regime is sometimes referred to as the Patent Term Guarantee Act of 1999. *See, e.g., Wyeth v. Dudas*, 580 F.Supp.2d 138, 139 (D.D.C. 2008).

are then limited to an "appeal in the case of rejection of any claim" or "to [an] amendment" of the application. *Id.* The RCE is one such amendment. Once a final rejection has issued, the applicant generally has up to six months to file an RCE before the application is abandoned. *See* 37 C.F.R. § 1.135. An RCE, which may consist of (but is not limited to) "an information disclosure statement, an amendment to the written description, claims, or drawings, new arguments, or new evidence in support of patentability," functions to continue the examination of the current application by reopening the prosecution. 37 C.F.R. § 1.114(b).

Once the PTO determines that the application contains patentable claims, the PTO will issue a "Notice of Allowance" that informs the applicant that he "is entitled to a patent under the law[.]" 37 C.F.R. § 1.311(a). The applicant must then pay the requisite fees within three months, otherwise the application will be deemed abandoned. *Id.* Even after the fee has been paid, up until the patent actually issues, the application may be withdrawn by either the PTO or the applicant. 37 C.F.R. § 1.313.

B. Patent Term Adjustments

Subsection 154(b) of Title 35 governs the determination and measurement of PTA. Paragraph (1) of this subsection, entitled "Patent term guarantees," sets forth three general guarantees designed to expedite the application, prosecution, and examination process. This paragraph also describes the various categories of events that generate PTA, i.e., events that result in the extension of the patent term.

First, subparagraph (A), entitled "Guarantee of prompt Patent and Trademark Office responses,"[9] extends the patent term if the PTO fails to carry out certain acts during the

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[9] It is well settled that "'the title of a statute and the heading of a section' are 'tools available for the resolution of a doubt' about the meaning of a statute." *Almendarez-Torres v. United States*,

prosecution and examination of the patent within prescribed timelines. For example, if the PTO takes more than four months to issue a patent once the "issue fee was paid" and "all outstanding requirements were satisfied," then PTA is granted on a day for day basis for each day longer than four months until the patent is issued. § 154(b)(1)(A)(iv).

Next, subparagraph (B), entitled "Guarantee of no more than 3-year application pendency," extends the patent term on a day for day basis "for each day after the end of that 3 year period until the patent is issued." § 154(b)(1)(B). Subparagraph (B) ensures that the patent prosecution and examination process proceeds expeditiously to preserve an approximately 17 year patent term measured from the date of issuance. Certain events, such as time consumed by an RCE or by an applicant requested delay, are "not included" in the measurement, and here the parties disagree as to whether these events are "not included" in the measurement of the three year period (Exelixis' position) or in the PTA calculation (the PTO's position).

Finally, subparagraph (C), entitled "Guarantee of adjustments for delays due to interferences, secrecy orders, and appeals," extends the patent term on a day for day basis for "each day of the pendency of the proceeding, order, or review[.]" § 154(b)(1)(C). Put simply, subparagraph (C) grants PTA for time consumed by certain special proceedings that may occur during the course of the prosecution and examination of the application.

The PTA awarded under paragraph (1) is subject to certain limitations set out in paragraph (2), entitled "Limitations." Subparagraph (A) of paragraph (2) makes clear that "to

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523 U.S. 224, 234 (1998) (quoting *Trainmen v. Baltimore & Ohio R. Co.*, 331 U.S. 519, 528–29 (1947)); *see also I.N.S. v. Nat'l Center for Immigrants' Rights, Inc.*, 502 U.S. 183, 189 (1991) ("the title of a statute or section can aid in resolving an ambiguity in the legislation's text"); *Reese v. United States*, 24 F.3d 228, 231 (Fed. Cir. 1994) (using the section title as an aid to resolving a statutory ambiguity); *United States v. Clawson*, 650 F.3d 530, 536 (4th Cir. 2011) (noting that the statute's "heading further supports [the court's] determination" of statutory meaning).

the extent that periods of delay . . . overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed." § 154(b)(2)(A).[10] In other words, the PTA calculation must not double count; the applicant may not receive more than one day of PTA for the same calendar day. Next, subparagraph (B) limits the granting of PTA for disclaimed patent terms. Finally, subparagraph (C), entitled "Reduction of period of adjustment," reduces PTA for time consumed by delays attributable to the patent applicant. This includes the reduction of PTA by "a period equal to the period of time during which the applicant failed to engage in reasonable efforts to conclude prosecution of the application." § 154(b)(2)(C)(i). The remaining paragraphs under subsection (b) set forth the procedures for the determination of PTA and for appeals of such determinations.

In this action, Exelixis contends that the PTO improperly calculated B delay by not providing a day for day PTA for time consumed by the RCE filed after the three year period had expired. In opposition, the PTO argues that the time consumed by an RCE is always excluded from the calculation of B delay because, in the PTO's view, any time consumed by an RCE is subtracted from the PTA awarded under subparagraph (B), regardless of when the RCE is filed.

III.

A case is ripe for summary judgment where "there 'is no genuine issue as to any material fact and the moving party is entitled to a judgment as a matter of law.'" *Wyeth*, 591 F.3d at 1369 (quoting Fed.R.Civ.P. 56(c)). Because in the present case both parties "perceive no genuine issues of material fact," there is only a legal determination to be made, namely whether the PTO's method for calculating PTA under § 154(b)(1)(B) is contrary to law. *See id.* The PTO's

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[10] *See Wyeth v. Kappos*, 591 F.3d 1364, 1368–72 (rejecting the PTO's "greater-of-A-or-B rubric" and holding that § 154(b)(2)(A) applies only where there is overlap between A delay and B delay).

determination of PTA is subject to judicial review under the Administrative Procedure Act. 35 U.S.C. § 154(b)(4)(A). Thus, a district court may only set aside the PTO's decision if it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). An agency abuses its discretion "where the decision is based on an erroneous interpretation of the law, on factual findings that are not supported by substantial evidence, or represents an unreasonable judgment in weighing relevant factors." *Star Fruits S.N.C. v. United States*, 393 F.3d 1277, 1281 (Fed. Cir. 2005); *Arnold Partnership v. Dudas*, 362 F.3d 1338, 1340 (Fed. Cir. 2004).

IV.

Analysis of the question presented properly begins with the plain language of the statute. As the Supreme Court has noted, "it is axiomatic that '[t]he starting point in every case involving construction of a statute is the language itself.'" *Landreth Timber Co. v. Landreth*, 471 U.S. 681, 685 (1985) (quoting *Blue Chip Stamps v. Manor Drug Stores*, 421 U.S. 723, 756 (1975) (Powell, J., concurring)).[11] Further, the Supreme Court has made clear that where "the statute's language is plain, 'the sole function of the courts is to enforce it according to its terms.'" *U.S. v. Ron Pair Enterprises, Inc.*, 489 U.S. 235, 241 (1989) (quoting *Caminettie v. United States*, 242 U.S. 470, 485 (1917)). The Supreme Court has warned, however, that there may be "rare cases [in which] the literal application of a statute will produce a result demonstrably at odds with the intentions of its drafters." *Ron Pair Enterprises*, 489 U.S. at 242 (quoting *Griffin v. Oceanic Contractors, Inc.*, 458 U.S. 564, 571 (1982)). It is only in those rare cases that "the intention of the drafters, rather than the strict language, controls." *Id.* And in the Federal Circuit, "only a 'most

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[11] *See also Wyeth*, 591 F.3d at 1369 ("As always, the starting point in every case involving construction of a statute is the language itself.") (internal quotation marks omitted).

extraordinary showing of contrary intentions' by Congress justifies a departure from the plain language of a statute." *Wyeth*, 591 F.3d at 1371 (quoting *Garcia v. United States*, 469 U.S. 70, 75 (1984)). Thus, a court must give a statute its plain language meaning unless that meaning clearly contradicts the drafter's intent.

Here, the plain language meaning of subparagraph (B) is clear, unambiguous, and in accord with both the statute's structure and purpose. Subparagraph (B) provides in pertinent part,

> Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to the failure of the United States Patent and Trademark Office to issue a patent within 3 years after the actual filing date of the application in the United States, not including:
>
> (i) any time consumed by continued examination of the application requested by the applicant under section 132(b);
>
> . . .
>
> the term of the patent shall be extended 1 day for each day after the end of that 3-year period until the patent is issued.

35 U.S.C. § 154(b)(1)(B). Simply put, the goal of this subparagraph, as its title indicates, is a "Guarantee of no more than 3-year application pendency." It accomplishes this goal by (i) starting a three year clock on the date the application is filed, (ii) tolling the running of this clock if, within the three year period, any of three events occur, including an RCE filing, and (iii) adding a day for day PTA to the patent term for any delay in the issuance of the patent after the three year clock, less any tolling, runs out. Thus, subparagraph (B) essentially describes two calculations. The first is a description of the calculation of the three year period: The three year clock beings to run on the date the application is filed and, except for three specific potential tolling events, including the filing of an RCE, the clock runs continuously until the three year period ends. In other words, the "not including" portion of subparagraph (B), followed by (i), (ii), and (iii), clearly and unambiguously modifies and pertains to the three year period and does not apply to, or refer to, the day for day PTA remedy. Subparagraph (B)'s second calculation is

simply a day for day addition to the PTA for every day beyond the end of the three year clock until the patent issues.

Especially notable about this reading of subparagraph (B), which is commanded by the provision's plain and unambiguous language, is that it does not address the filing of an RCE after the expiration of the three year clock. To be sure, the provision makes clear that the clock is tolled for the processing of an RCE filed before the three year clock runs out, but the provision does not refer to or mention RCE's filed after the three year clock has run. Instead, subparagraph (B) makes clear that once the three year clock has run, PTA is to be awarded on a day for day basis regardless of subsequent events.

Also notable of subparagraph (B) is that the reading compelled by its plain language is firmly supported by § 154(b)'s structure and purpose. The statute's purpose is to ensure that an applicant is provided with a PTA remedy for delays in examination and processing attributable to the PTO and to reduce any PTA by delays attributable to the applicant. Significantly, § 154(b) does not treat an RCE filing as applicant delay; instead applicant delay is treated in § 154(b)(2)(C), which is captioned "Reduction of period of adjustment"[12] and does not refer to RCE's. The RCE is treated only in subparagraph (B), which specifies that an RCE filed during the running of the three year clock tolls the running of that clock while the RCE is processed. In other words, the statute does not consider an applicant's submission of an RCE as "applicant delay" that warrants reduction under § 154(b)(2)(C); rather, the statute simply treats the time devoted to an RCE as time that should not be counted against the PTO in the running of the three year clock.

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[12] Subsection (2)(C) addresses situations where applicants have "failed to engage in reasonable efforts to conclude prosecution of the application" and, as a result, the PTA that would otherwise be added to the patent term is reduced. § 154(b)(2)(C).

In summary, the plain and unambiguous language of subparagraph (B) requires that the time devoted to an RCE serves to toll the running of the three year clock, if the RCE is filed within the three year period; subparagraph (B) does not address RCE's filed after the running of the three year period nor does it require that the time consumed by an RCE filed after the running of the three year clock be deducted from the PTA. Put simply, RCE's have no impact on the PTA after the three year deadline has passed[13] and subparagraph (B) clearly provides no basis for any RCE's to reduce PTA; instead, RCE's operate only to toll the three year guarantee deadline, if, and only if, they are filed within three years of the application filing date. Thus, the PTO erred in construing subparagraph (B) to the contrary. In doing so, the PTO, in essence, construed subparagraph (B) to punish the applicant for filing the RCE. Yet there is no basis for reading subparagraph (B) in this manner. Indeed, the PTO properly regards the RCE not as an occasion to punish the applicant, but as a "valuable tool in the patent prosecution process."[14] Nor does the PTO list an RCE as one of 11 enumerated applicant delays.[15] In sum, the PTO in this case incorrectly treats an RCE as a punitive measure, that is a measure aimed at punishing Exelixis by reducing PTA—rather than as a "valuable tool in the patent prosecution process"—where, as here, the RCE was filed after the expiration of the three year clock. Accordingly, the PTO's calculation of B delay must be set aside as "not in accordance with law" and "in excess of [its] statutory . . . authority" pursuant to 5 U.S.C. § 706(2)(A) and (C). *See also Wyeth*, 591 F.3d at 1372 (holding that because, in the context of § 154(b)(2)(C), § "154(b)'s language is clear,

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[13] A possible exception to this may occur where an RCE in particular circumstances not present here, is properly categorized as applicant delay under § 154(b)(2)(C).

[14] Bob Stoll, *RCE Filings: The Facts*, Director's Forum: David Kappos' Public Blog, Jul. 26, 2010, http://www.uspto.gov/blog/director/entry/rce_filings_the_facts.

[15] *See* 37 C.F.R. § 1.704

unambiguous, and intolerant of the PTO's suggested interpretation," the Federal Circuit "accords no deference to the PTO's [interpretation]").

The PTO offers several arguments in support of its interpretation, none of which is persuasive.[16] First, the PTO argues that a proper reading of subparagraph (B) requires the insertion of the word "then" prior to the phrase "not including" that is followed by (i), (ii), and (iii). According to the PTO, inserting the word "then" at that point allows subparagraph (B) to be read so that time consumed by an RCE is deducted from the day for day remedy for the PTO's failure to meet the three year guarantee deadline. The short and dispositive answer to this argument is that the word "then" does not appear in the statute and the PTO's insertion of the word in its reading is not a construction of the provision but rather a re-writing of it. Neither courts nor agencies may change or alter the plain language and meaning of a statute because of a belief, however well founded, that the statute would be improved thereby.[17] In any event, there is no persuasive reason to conclude that the statute would be improved by changing the language as the PTO proposes. This is so because the statute and the PTO[18] do not regard RCE's as undesirable devices for which the applicant should be punished. Put differently, § 154(b) does not treat an RCE as an applicant's failure "to engage in reasonable efforts to conclude prosecution of the application" under § 154(b)(2)(C)(i). In effect, RCE's are something for

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[16] Although the plain language of subparagraph (B) may result in the PTO awarding C delay less often, this simply does not, as the PTO argues, render subparagraph (C) superfluous.

[17] *See Badaracco v. Comm'r of Internal Revenue*, 464 U.S. 386, 398 (1984) ("Courts are not authorized to rewrite a statute because they might deem its effects susceptible of improvement."); *see also Allergan, Inc. v. Alcon Laboratories, Inc.*, 324 F.3d 1322, 1346 (Fed. Cir. 2003) ("it is the function of Congress, not the courts, to shape legislation in accordance with policy goals").

[18] *See* Stoll, *supra* n. 14.

which the three year clock should be tolled, but not something that reduces the PTA. To avoid the problem presented in the present case—an RCE filed after the three year clock has expired—the PTO should aim to issue any notice of rejection before the expiration of the three year period and then, by regulation, require applicants to file RCE's in response to such notices within 30 days.

Next, the PTO argues that its construction of subparagraph (B) deserves *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944), deference.[19] To be sure, when statutes, as not the case here, are unclear or ambiguous, *Skidmore* deference to the PTO's interpretation might be appropriate.[20] Again, the short answer here is that *Skidmore* deference is unwarranted, when, as here, the statute is unambiguous.

Finally, the PTO argues that its reading of subparagraph (B) avoids absurd results. Under the PTO's view, the plain language of subparagraph (B) may lead to disparate treatment of some similarly situated applicants, depending on whether the applicant files the RCE before or after the expiration of the three year period. But such disparities arise only at the margins and the

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[19] For reasons the PTO did not make clear, the PTO explicitly declined to assert or claim *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984), deference, notwithstanding the existence of a regulation—37 C.F.R. § 1.703—setting forth the very reading of subparagraph (B) that it advances here. In any event, *Chevron* deference is not appropriate because the statute is not ambiguous as written. Moreover, the regulation has the effect of altering the PTA and the patent term, which is a substantive alteration that the PTO is arguably unauthorized to make. *See* § 154(b)(3)(A) ("The Director shall prescribe regulations establishing procedures for the application for and determination of patent term adjustments under this subsection.") (emphasis added).

[20] Indeed, it appears that in the Federal Circuit, *Skidmore* deference carries more force than in the other circuits. *Compare Cathedral Candle Co. v. U.S. Intern'l Trade Com'n*, 400 F.3d 1352, 1366 (Fed. Cir. 2005) (interpreting *Skidmore* and subsequent cases to require deference "even if we might not have adopted that construction without the benefit of the agency's analysis") *with Shipbuilders Council of Am. V. U.S. Coast Guard*, 578 F.3d 234, 241 (4th Cir. 2009) ("Under the *Skidmore* standard, the court defers to an agency interpretation only if and to the extent that it is persuasive.").

Federal Circuit rejected similar arguments in *Wyeth*, where it explained that "[r]egardless of the potential of the statute to produce slightly different consequences for applicants in similar situations, this court does not take upon itself the role of correcting all statutory inequities." *Wyeth*, 591 F.3d at 1370. Indeed, in subparagraph (B), Congress "has put a policy in effect that this court must enforce, not criticize or correct." *See id.* It is also worth noting that the disparate treatment of applicants in these circumstances can be minimized by the PTO because the PTO controls the timing of a notice of rejection, which is a typical event that causes an applicant to file an RCE. Thus, if the PTO takes steps to issue notices of rejection well within the running of the three year clock and also requires RCE's to be filed within a fixed number of days after receipt of such notice—also within the three year period, then the time devoted to RCE's will generally count against the running of the clock and applicants will not be disparately treated.

V.

In sum, the plain and unambiguous language of subparagraph (B) requires that the time devoted to an RCE tolls the running of the three year clock if the RCE is filed within the three year period. And, put simply, RCE's have no impact on PTA if filed after the three year deadline has passed. The PTO's arguments to the contrary are not persuasive and, accordingly, the PTO's interpretation of subparagraph (B) must be set aside as "not in accordance with law" and "in excess of [its] statutory . . . authority" pursuant to 5 U.S.C. § 706(2)(A) and (C). The proper measure of B delay in the present case is from January 15, 2011 (three years after the application filing date) to August 2, 2011 (the date the patent issued). Thus, the B delay PTA for the '622 patent is properly calculated as 199 days.

An appropriate Order will issue.

T. S. Ellis, III
United States District Judge

Alexandria, VA
November 1, 2012

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
Alexandria Division

EXELIXIS, INC.,	)	
Plaintiff,	)	
	)	
v.	)	**Case No. 1:12cv96**
	)	
HON. DAVID J. KAPPOS, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office,	)	
Defendant.	)	

ORDER

For good cause,

It is hereby **ORDERED** that the memorandum opinion (doc. 29) is **AMENDED** to insert the following footnote on page 14 at the end of the sentence that reads, "The short and dispositive answer to this argument is that the word "then" does not appear in the statute and the PTO's insertion of the word in its reading is not a construction of the provision but rather a rewriting of it":

> Footnote: Nor is the legislative history of any avail to the PTO; this history does not expressly address the question presented and is, at best, ambiguous. Fairly read, the legislative history simply repeats what subparagraph (B) clearly states. See H.R. Rep. No. 106-464, at 126 ("Any periods of time . . . consumed [by an RCE] . . . shall not be considered delay by the USPTO and shall not be counted for purposes of determining whether the patent issued within three years from the actual filing date"). In any event, legislative history, however interpreted, cannot trump clear and unambiguous statutory language. *See Mohamed v. Palestinian Authority*, 132 S.Ct. 1702, 1709 (2012) ("reliance on legislative history is unnecessary in light of the statute's unambiguous language") (internal quotation marks and citation omitted); *United States v. Gonzales*, 520 U.S. 1, 6 (1997) ("Given the straightforward statutory command, there is no reason to resort to legislative history.").

In all other respects, the memorandum opinion remains unchanged.[1]

The Clerk is directed to send a copy of this Order to all counsel of record.

Alexandria, VA
November 6, 2012

T. S. Ellis, III
United States District Judge

[1] The footnote being added was omitted inadvertently.

EXHIBIT 4

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

NOVARTIS AG, et al.,	)	
Plaintiffs,	)	
v.	)	**Civil Action No. 10-cv-1138 (ESH)**
HON. DAVID J. KAPPOS,	)	**(Consolidated)**
Defendant.	)	

MEMORANDUM OPINION

Plaintiffs Novartis AG and Novartis Vaccines and Diagnostics, Inc. ("Novartis") have sued David J. Kappos, the Under Secretary of Commerce for Intellectual Property and the Director of the U.S. Patent and Trademark Office ("PTO"). Plaintiffs bring this suit under 35 U.S.C. § 154, and the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 701 *et seq.*, claiming that defendant improperly determined the amount of patent term adjustment to which they are entitled. Before the Court are plaintiffs' Motion for Summary Judgment and defendant's Cross Motion for Summary Judgment. For the reasons set forth below, plaintiffs' motion will be granted in part and denied in part, and defendant's motion will be granted in part and denied in part.

BACKGROUND

I. LEGAL FRAMEWORK

Prior to 1994, U.S. patents were granted for a term of seventeen years from the date the patent issued. In 1994, Congress adjusted the term of a U.S. patent to twenty years from the date

the application was filed to bring the U.S. in line with other countries' patent terms. However, because the examination of a patent application often takes more than three years from filing to the issuance of a patent, this meant that many patentees received effective patent terms of less than the historical seventeen-year period. Thus, in 1999, Congress amended the Patent Act by creating patent term adjustments ("PTA") to extend patent terms in response to unreasonable delays in the examination of a patent application. *See* 35 U.S.C. § 154(b).

The Patent Act created several types of PTA, two of which are at issue here. First, a patentee can accrue PTA if the PTO fails to take certain specified actions within fixed windows of time. *See* 35 U.S.C. § 154(b)(1)(A). For example, if the PTO does not issue an office action responding to a patent application within 14 months after the application was filed, the patentee will be awarded one day of PTA for every day until the first office action is issued. *Id.* This type of PTA is known as "A Delay." The PTO notifies the patentee of the amount of A Delay that has been awarded when it issues the Notice of Allowance. Because the Notice of Allowance is sent well before a patent is actually granted, the determination of A Delay is known as a Pre-Issuance Determination.

A second type of PTA accrues if the PTO fails to issue a patent within three years of the filing of the application. *See* 35 U.S.C. § 154(b)(1)(B). This type of PTA is known as "B Delay." Specifically, § 154(b)(1)(B) provides that:

> if the issue of an original patent is delayed due to the failure of the [PTO] to issue a patent within 3 years after the actual filing date of the application in the United States, not including-
>
> (i) any time consumed by continued examination of the application requested by the applicant under section 132(b);
>
> (ii) any time consumed by a proceeding under section 135(a), any time consumed by the imposition of an order under section 181, or any

> time consumed by appellate review by the Board of Patent Appeals and Interferences or by a Federal court; or
>
> (iii) any delay in the processing of the application by the United States Patent and Trademark Office requested by the applicant except as permitted by paragraph (3)(C),
>
> the term of the patent shall be extended 1 day for each day after the end of that 3-year period until the patent is issued.

Id.

The PTO has promulgated two final rules interpreting the proper calculation of B Delay under § 154(b)(1)(B). First, 37 C.F.R. § 1.702(b) states that the patent term shall be adjusted if the issuance of the patent was delayed due to the failure of the PTO to issue a patent within three years after the filing date, "but not including: (1) any time consumed by continued examination of the application under 35 U.S.C. § 1.703(b)." Second, 37 C.F.R. § 1.703(b) states that the period of adjustment under § 1.702(b) is to be the number of days beyond three years from the filing date, but not including the number of days between the filing of a request for continued examination ("RCE") and the date the patent is issued. In other words, § 1.703(b) provides that: (1) patentees cannot accrue B Delay for time consumed by an RCE, regardless of when it was filed, and (2) "time consumed by" an RCE includes all of the time from the filing of the RCE to the issuance of the patent. Because B Delay accrues until the actual date of issuance, the PTO does not determine the proper amount of B Delay until the patent is granted.

After determining the proper amount of A and B Delay, the PTO must determine the extent of any overlap between the two types of delay. The method of determining A/B Delay Overlap was changed in response to the Federal Circuit's decision in *Wyeth v. Kappos*, 591 F.3d 1364 (Fed. Cir. 2010). Prior to *Wyeth*, the PTO interpreted the period

of B Delay to include the entire time between the filing of an application and the issuance of a patent more than three years later. Thus, if a patent took longer than three years to issue, any A Delay that occurred during the pendency of the application by definition overlapped with the period of B Delay, and was not awarded to the patentee as PTA. As the Federal Circuit explained, "[u]sing this framework, the PTO use[d] either the greater of the A delay or B delay to determine the appropriate adjustment, but never combine[d] the two." *Wyeth*, 591 F.3d at 1368. In *Wyeth*, the Federal Circuit held that the PTO's interpretation of the overlap provision was erroneous; A Delay and B Delay should be aggregated so long as that aggregation would not require counting the same calendar day twice. *See id.* at 1369-70.

After the Federal Circuit's decision in *Wyeth*, the PTO announced that it would not seek further review of that decision and would implement the court's interpretation of A/B Delay Overlap when determining the appropriate amount of PTA for issued patents beginning on March 2, 2010. (AR166-67.) The PTO also announced that it would permit recalculation of PTA for patents issued prior to March 2, 2010, so long as the request for reconsideration was filed within 180 days of the grant of the patent. (AR170.) Thus, only patents that had been granted within the 180 days prior to that announcement were eligible for a recalculation of their PTA using the new post-*Wyeth* interpretation.

Because the overlap determination depends on the amount of B Delay, it is also done at the time the patent is granted. The final determination of PTA, which factors in just A Delay but also B Delay and any overlap between A and B Delay, is therefore known as an Issuance Determination.

II. PROCEDURAL HISTORY

On July 6, 2010, Novartis filed suit, alleging that the PTO had improperly calculated the amount of PTA to which eleven of its patents were entitled. (Complaint [ECF No. 1].) Novartis argued first that the PTO acted improperly in refusing to apply the post-*Wyeth* interpretation of A/B Delay Overlap to patents granted prior to September 2, 2009 ("the *Wyeth* Claim"). Second, Novartis challenged the PTO's interpretation of the effect of an RCE on the determination of B Delay ("the RCE Claim"). On February 16, 2012, this Court ordered that this case be consolidated with three other matters—*Novartis v. Doll*, No. 09-cv-1203, *Novartis v. Kappos*, No. 11-cv-0659, and *Novartis v. Kappos*, No. 11-cv-0821—all of which raise the same legal issues. Given the consolidation of the four cases, the PTA determinations for twenty-three of Novartis' patents are now at issue.

Plaintiffs filed a Motion for Summary Judgment on May 16, 2012. ([Dkt. No. 35] ("Pls.' Mot.").) Defendant then filed a Cross Motion for Summary Judgment and Opposition to plaintiffs' motion on June 18, 2012. ([Dkt. No. 38] ("Def.'s Mot.").) On July 18, 2012, plaintiffs filed an Opposition to defendant's Cross Motion and a Reply to defendant's Opposition to its Motion. ([Dkt. No. 40] ("Pls.' Reply").) And finally, on August 20, 2012, defendant filed a Reply to plaintiff's Opposition. ([Dkt. No. 42] ("Def.'s Reply").)

ANALYSIS

I. LEGAL STANDARDS

A. Judicial Review of Patent Term Adjustments

The APA provides judicial review of an agency action to a party who has suffered a legal wrong because of that action. 5 U.S.C. § 702. The APA gives the court authority to "decide all

relevant questions of law, interpret constitutional and statutory provisions, and determine the meaning or applicability of the terms of an agency action." 5 U.S.C. § 706. It further provides that the reviewing court shall set aside an agency action that is found to be "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," or "in excess of statutory jurisdiction, authority, or limitations." *Id.*

The arbitrary and capricious standard "presumes the validity of agency action, requiring [the court] to determine whether the agency has considered the relevant factors and 'articulate[d] a rational connection between the facts found and the choice made.'" *AT&T Corp. v. FCC*, 220 F.3d 607, 616 (D.C. Cir. 2000) (quoting *Motor Vehicle Mfrs. Ass'n of the U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983)). The court "may reverse only if the agency's decision is not supported by substantial evidence, or the agency has made a clear error in judgment." *Kisser v. Cisneros*, 14 F.3d 615, 619 (D.C. Cir. 1994).

B. Motion for Summary Judgment

Normally, a motion for summary judgment under Rule 56 shall be granted if the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(a), (c); *see also Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247 (1986). "In a case involving review of a final agency action under the [APA], however, the standard set forth in Rule 56(c) does not apply because of the limited role of a court in reviewing the administrative record." *Sierra Club v. Mainella*, 459 F. Supp. 2d 76, 89 (D.D.C. 2006) (citation omitted).

"Under the APA, it is the role of the agency to resolve factual issues to arrive at a decision that is supported by the administrative record, whereas 'the function of the district court is to determine whether or not as a matter of law the evidence in the administrative record permitted the agency to make the decision it did.'" *Id.* at 90 (quoting *Occidental Eng'g Co. v. INS*, 753 F.2d 766, 769-70 (9th Cir. 1985)). Thus, "when an agency action is challenged" solely with "arguments about the legal conclusion to be drawn about the agency action," then the case on review presents only a question of law and can be resolved on the administrative record pursuant to a motion for summary judgment. *Marshall Cnty. Health Care Auth. v. Shalala*, 988 F.2d 1221, 1226 (D.C. Cir. 1993). In that instance, a "district court[ ] reviewing agency action under the APA's arbitrary and capricious standard do[es] not resolve factual issues, but operate[s] instead as [an] appellate court[ ] resolving legal questions." *James Madison Ltd. by Hecht v. Ludwig*, 82 F.3d 1085, 1096 (D.C. Cir. 1996).

In this case, the only issue for review is a legal question as to whether the PTO's determination of PTA for each of Novartis' patents was a valid and appropriate exercise of agency discretion.

C. Standard of Review

In answering this question, it is necessary to determine what level of deference the PTO's determination is entitled to. Under *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), "where Congress has authorized an agency to promulgate substantive rules under a statute it is charged with administering," the court "must uphold the agency's interpretation of an ambiguity or omission in that statute if the interpretation is a reasonable one." *Merck & Co., Inc. v. Kessler*, 80 F.3d 1543, 1549 (Fed. Cir. 1996) (citing *Chevron*, 467

U.S. at 842-45). However, the Federal Circuit has previously determined that the PTO does not have the authority to issue substantive rules, only procedural regulations regarding the conduct of proceedings before the agency. *See Merck*, 80 F.3d at 1549-50. Indeed, 35 U.S.C. § 154(b)(3)(A) limits the PTO's authority to prescribing "regulations establishing procedures for the application for and determination of patent term adjustments." 35 U.S.C. § 154(b)(3)(A). Thus, the PTO's determination is not entitled to *Chevron* deference. *See Merck*, 80 F.3d at 1549-50; *Wyeth v. Dudas*, 580 F. Supp. 2d 138, 141 (D.D.C. 2008).

Instead, the PTO is only entitled to deference under *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944), which depends upon "the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade, if lacking power to control." *Id.* at 140; *see also Merck*, 80 F.3d at 1550. In other words, a court will only defer to an agency interpretation if, among other things, "the agency's position constitutes a reasonable conclusion as to the proper construction of the statute." *See Cathedral Candle Co. v. United States Int'l Trade Comm'n*, 400 F.3d 1352, 1366 (Fed. Cir. 2005).

II. TIMELINESS

Challenges to PTA determinations are governed by 35 U.S.C. § 154(b)(4)(A). That section provides:

> An applicant dissatisfied with a determination made by the Director under paragraph (3) shall have remedy by a civil action against the Director filed in the United States District Court for the District of Columbia within 180 days after the grant of the patent.[1]

[1] For complaints filed on or after September 16, 2011, the U.S. District Court for the Eastern District of Virginia now has jurisdiction over actions under 35 U.S.C. § 154(b). Pub. L. 112-29 at § 9(a), 125 Stat. 284, 316.

35 U.S.C. § 154(b)(4)(A). Defendant does not dispute that timely complaints were filed with respect to three of the Novartis Patents—U.S. Patent Nos. 7,807,155 ("the '155 patent"), 7,968,518 ("the '518 patent"), and 7,973,031 ("the '031 patent"). (Def.'s Mot. at 10.) However, the PTO asserts that because the complaints relating to the remaining patents were filed more than 180 days after the grant of each of those patents, Novartis is foreclosed from seeking additional PTA for those patents. (*Id.* at 10-11.)

As an initial matter, Novartis asserts that the 180-day limitation of § 154(b)(4)(A) does not apply to its claims. By its terms, § 154(b)(4)(A) applies to determinations "under paragraph (3)" of that section. Novartis asserts that § 154(b)(3) governs only Pre-Issuance PTA Determinations, meaning determinations of A Delay. (Pls.' Mot. at 31-32.) Novartis points to several portions of that subsection to support its position. For example, § 154(b)(3)(B)(i) states that: "the Director shall . . . make a determination of the period of any patent term adjustment under this subsection, and shall transmit a notice of that determination *with the written notice of allowance* under section 151." 35 U.S.C. § 154(b)(3)(B)(i) (emphasis added). Because neither B Delay nor A/B Overlap has been determined at the time a Notice of Allowance is issued, Novartis contends that this section should not apply to challenges to those determinations. (*Id.*) Similarly, § 154(b)(3)(D) states that the Director "shall proceed to grant the patent *after* completion of the Director's determination of a patent term adjustment under the procedures established under this subsection." 35 U.S.C. § 154(b)(3)(D) (emphasis added). In Novartis' view, the fact that the statute suggests that the PTA determination must be made prior to the grant of the patent indicates that it relates only to Pre-Issuance Determinations. (*Id.* at 32.) Thus, because no Pre-Issuance PTA Determinations are implicated here, Novartis argues that 35

U.S.C. § 154(b)(3) is irrelevant, and the 180-day limitations period of 35 U.S.C. § 154(b)(4)(A) does not apply. Instead, according to Novartis, the general six-year statute of limitations of the APA (*see* 28 U.S.C. § 2401(a)) applies to Novartis' appeal of Issuance PTA Determinations. (*Id.* at 34.)

The Court disagrees. Section 154(b)(3) is entitled "Procedures for patent perm adjustment determination" and is the only section of the statute to address the PTO's procedures for determining PTA. From its plain language, it is clearly intended to relate to all PTA determinations, regardless of when they occur. Indeed, the very language Novartis points to—that the Director "shall proceed to grant the patent after completion of the Director's determination"—clearly requires that the Director make a full determination of all types of PTA because both A Delay and B Delay (as well as any overlap between the two) must be determined before the patent is granted.

In addition to being consistent with the plain meaning of the statute, this interpretation avoids absurd results. Congress clearly intended to include strict controls on judicial review of PTA determinations. Under Novartis' interpretation, only Pre-Issuance Determinations would be subject to those controls, while the final, complete PTA determinations that accompany an issued patent would not. Instead, a patentee would have 180 days in which to challenge the calculation of A Delay but six years in which to challenge B Delay and A/B Delay Overlap.

In reaching this conclusion, this Court is persuaded by the recent opinion in *Janssen Pharmaceutica N.V. v. Kappos*, 844 F. Supp. 2d 707 (E.D. Va. 2012), that 35 U.S.C. § 154(b)(4)(A) provides the exclusive means for judicial challenges to the PTO's PTA determinations. *Id.* at 713. That court held:

> [I]n a case in which a patentee is challenging the number of days of PTA calculated by the USPTO, whether that calculation occurred before the patent was issued or afterwards, such a decision is governed by §§ 154(b)(3) and (b)(4)(A). In other words, any challenge to a PTA determination is governed by § 154(b)(4)(A).

Id. The court reasoned that a contrary holding would be "entirely inconsistent with the Congressional intent plain on the face of the statute—to strictly limit the forum and timing for seeking judicial review of these very specific USPTO decisions." *Id.* As such, the 180-day limitation prescribed by that section applies to the PTA determinations at issue here.

A. Ordinary Tolling

Judicial review of agency actions is ordinarily tolled until the agency action is final. *See Clifton Power Corp. v. FERC*, 294 F.3d 108, 110 (D.C. Cir. 2002) (citing *Interstate Commerce Comm'n v. Bhd. of Locomotive Eng'rs*, 482 U.S. 270, 284 (1987)). "A request for administrative reconsideration renders an agency's otherwise final action non-final with respect to the requesting party." *Clifton*, 294 F.3d at 110 (citing *United Transp. Union v. Interstate Commerce Comm'n*, 871 F.2d 1114, 1116 (D.C. Cir. 1989)). Thus, judicial review of an agency action must be tolled during the period of agency reconsideration. As the Supreme Court explained in *Locomotive Engineers*:

> [W]here a petition for reconsideration has been filed within a discretionary review period specifically provided by the agency (and within the period allotted for judicial review of the original order) . . . the petition tolls the period for judicial review of the original order, which can therefore be appealed to the courts directly after the petition for reconsideration is denied.

482 U.S. at 279.

With respect to U.S. Patent No. 7,470,792 ("the '792 patent"), Novartis filed a petition for PTA reconsideration with the PTO within two months of issuance, as directed by 37 C.F.R. §

1.705(d), raising the same claim that is now before this Court. Within 180 days of the PTO's denial of reconsideration (but more than 180 days after the issuance of the patent), Novartis filed suit in this court. Thus, Novartis argues that the 180-day limitation period should have been tolled by its filing of a petition for reconsideration, rendering its claim with respect to the '792 patent timely.[2]

The PTO asserts that the ordinary tolling rule does not apply to § 154(b)(4)(A). First, the PTO argues that applying the normal tolling rule to § 154(b)(4)(A) would read out the language "after the grant of the patent" from the statute. (Def.'s Mot. at 27.) However, it is well established that "a statutory provision setting the limitations period is *not* incompatible with a tolling rule." *Bristol-Myers Squibb Co. v. Kappos*, 841 F. Supp. 2d 238, 243, *motion for reconsideration denied*, 2012 WL 4127636 (D.D.C. Sept. 20, 2012). Indeed, this Circuit has applied the ordinary tolling rule to numerous statutes providing for specific limitations periods that are triggered by specified dates. *See, e.g.*, *Columbia Falls Aluminum Co. v. EPA*, 139 F.3d 914, 920-21 (D.C. Cir. 1998) (tolling 90-day limitations period beginning from the date of the challenged promulgation or denial); *Los Angeles SMSA Ltd. P'ship v. FCC*, 70 F.3d 1358, 1359 (D.C. Cir. 1995) (tolling a 30-day limitation period beginning on "the date upon which public notice is given of the decision or order complained of"). Thus, the mere fact that § 154(b)(4)(A)

[2] The PTO correctly points out that Novartis did not allege that ordinary tolling applied in its Second Amended Complaint. (Def.'s Mot. at 26 n. 10.) Although it remains an "open question" in the D.C. Circuit as to "whether the Federal Rules permit parties to impliedly consent to 'try' issues not raised in their pleadings through summary judgment motions," the Court will follow the majority of circuits that do allow constructive amendment of the pleadings under Rule 15(b) through summary judgment motions. *See Turner v. Shinseki*, 824 F. Supp. 2d 99, 122 n.23 (D.D.C. 2011) (collecting cases).

sets a specific date from which the 180-day limitation period is to run—the date the patent is granted—does not render the general tolling rule inapplicable.

Next, the PTO argues that the language of § 154(b)(4)(A) suggests that Congress clearly intended "to depart from the ordinary judicial treatment of agency orders under reconsideration." (Def.'s Mot. at 27-28 (quoting *Stone v. INS*, 514 U.S. 386, 393 (1995)).) Specifically, the PTO argues that by tying the 180-day limitation to the date of patent grant and expressly providing that the issuance of the patent should proceed regardless of any reconsideration sought by the applicant, *see* 35 U.S.C. § 154(b)(3)(D), Congress clearly intended to override the application of the general tolling rule. (*Id.* at 28.)

The same argument by the PTO was rejected in *Bristol-Myers Squibb*, 841 F. Supp. 2d at 244-45. The Court concluded defendant's arguments do not "support a conclusion that Congress intended for the ordinary tolling rule not to apply to Section 154(b)(4)(A)." *Id.* at 244. To the contrary, § 154(b)(4)(A) expressly states that Chapter 7 of Title 5—which includes the general tolling rule—applies to any actions arising under that section, a fact this Court recently noted "indicates that Congress affirmatively intended for the tolling rule to apply to judicial review of patent term adjustment determinations." *Bristol-Myers Squibb*, 2012 WL 4127636, at *6. Thus, nothing about § 154(b)(4)(A) "direct[s] this Court to take any action inconsistent with the normal tolling rule." *Bristol-Myers Squibb*, 841 F. Supp. 2d at 245.

Because the Court holds that the general tolling rule applies, and because Novartis filed its complaint with respect to the '792 patent within 180 days after the denial of its petition for reconsideration, Novartis' claim with respect to that patent was timely filed.

B. Equitable Tolling

With respect to the nineteen remaining patents that were neither timely filed nor susceptible to ordinary tolling, Novartis argues that the 180-day limitations period should be equitably tolled.

The Court must first determine if § 154(b)(4)(A) is susceptible to equitable tolling. That question turns on whether the statute is jurisdictional in nature. The law on what constitutes a "jurisdictional" statute is, to say the least, far from clear. *See, e.g.*, *Gonzalez v. Thaler*, 132 S. Ct. 641, 648 (2012) ("Recognizing our 'less than meticulous' use of the term in the past, we have pressed a stricter distinction between truly jurisdictional rules, which govern 'a court's adjudicatory authority,' and nonjurisdictional 'claim-processing rules,' which do not.") (quoting *Kontrick v. Ryan*, 540 U.S. 442, 454-55 (2004)); *Grocery Mfrs. Ass'n v. EPA*, 693 F.3d 169, 183 (D.C. Cir. 2012) ("In recent years, the terminology of jurisdiction has been put under a microscope at the Supreme Court. And the Court has not liked what it has observed—namely, sloppy and profligate use of the term 'jurisdiction' by lower courts and, at times in the past, the Supreme Court itself.") (Kavanaugh, J., dissenting).

In light of these recent admonishments to construe the meaning of "jurisdictional" narrowly, it is perhaps more prudent to conclude that § 154(b)(4)(A) should be viewed as a "claim-processing rule"—one that "seek[s] to promote the orderly progress of litigation by requiring that the parties take certain procedural steps at certain specified times," *Henderson v. Shinseki*, 131 S. Ct. 1197, 1203 (2011), and therefore, it is entitled to a "rebuttable presumption in favor of equitable tolling." *Holland v. Florida*, 130 S. Ct. 2549, 2560 (2010) (internal

quotation marks omitted). The Court, however, need not resolve this knotty question, because it finds that § 154(b)(4)(A) should not be equitably tolled under the circumstances of this case.

Equitable tolling is available to a petitioner who has been diligent in pursuing his rights, but for whom some extraordinary circumstance stood in the way and prevented timely filing. *Holland*, 130 S. Ct. at 2562. The decision to equitably toll a statute of limitations is made on a "case-by-case" basis depending on the facts of the case. *Id.* at 2563.

With respect to its *Wyeth* Claim, Novartis argues first that it lacked knowledge of its claim until the Federal Circuit's decision on January 7, 2010, in *Wyeth* changed the law with respect to A/B Delay Overlap. (Pls.' Mot. at 48-49.) Additionally, Novartis argues that it reasonably relied on the PTO's longstanding and consistent use of its pre-*Wyeth* method of calculating A/B Delay Overlap; according to Novartis, up until the *Wyeth* decision forced the PTO to use the correct interpretation of A/B Delay Overlap, Novartis reasonably believed that it would have been futile to file a lawsuit appealing the PTO's PTA determinations under that method of calculation. (*Id.*) Thus, Novartis suggests that the 180-day limitation should have been equitably tolled until the PTO's January 20, 2010 announcement that it would not seek further appellate review of the Federal Circuit's *Wyeth* decision.

With respect to its RCE Claim, Novartis goes even further, asserting that because no federal court has yet ruled on the viability of this claim, the statute of limitations has not yet begun to run. (*Id.* at 49.) Novartis insists that it was not until this claim was raised by Abbott Laboratories in *Abbott v. Kappos*, 10-cv-1853 (D.D.C.), filed on October 29, 2010, that Novartis even became aware that this was a possible claim. (*Id.*)

Novartis' arguments are unpersuasive. In effect, Novartis' position amounts to a contention that the statute of limitations should not begin to run until such time as a federal court has actually ruled on and upheld the very claims they seek to pursue. But of course, Novartis was free to raise the same issues that Wyeth and Abbott Laboratories raised in their lawsuits within the 180 days after their patents were granted. As this Circuit has previously noted:

> The only sure way to determine whether a suit can be maintained is to try it. The application of the statute of limitations cannot be made to depend upon the constantly shifting state of the law, and a suitor cannot toll or suspend the running of the statute by relying upon the uncertainties of controlling law. It is incumbent upon him to test his right and remedy in the available forums. These suits were not commenced until through the labor of others the way was made clear.

Commc'ns Vending Corp. of Arizona, Inc. v. FCC, 365 F.3d 1064, 1075 (D.C. Cir. 2004) (quoting *Fiesel v. Bd. of Educ.*, 675 F.2d 522, 524-25 (2d Cir. 1982)). It is of no moment that the PTO had consistently applied its pre-*Wyeth* interpretation of A/B Delay Overlap; the question is not what the PTO would have done in response to a request for reconsideration, but rather what a federal court would have done in reviewing the PTO's interpretation. That was both unasked and unanswered until Wyeth raised exactly this issue in its lawsuit, just as Novartis was free to do at any point within 180 days of its patents being granted.

Regardless, contrary to Novartis' argument, a change in law is not such an extraordinary circumstance as to justify the application of equitable tolling. *See Nihiser v. White*, 211 F. Supp. 2d 125, 130-31 (D.D.C. 2002). Indeed, this case is analogous to *Venture Coal Sales Co. v. United States*, 370 F.3d 1102 (Fed. Cir. 2004), in which Venture Coal argued that its injury from the Coal Sales Tax was "inherently unknowable" until the tax was held unconstitutional in *Ranger Fuel Corp. v. United States*, 33 F. Supp. 2d 466 (E.D. Va. 1998). *See Venture Coal*, 370

F.3d at 1107. The Federal Circuit rejected that argument and noted that, just like Novartis here, Venture Coal argued "not that it lacked *sufficient facts* on which it could sue, but rather it did not know the *legal theory* on which its refund claim might succeed." *Id.*; *see also Nihiser*, 211 F. Supp. 2d at 131 ("[A]ll the relevant facts were known. It was the meaning of the law that was misunderstood.") (quoting *Catawba Indian Tribe of South Carolina v. United States*, 982 F.2d 1564, 1572 (Fed. Cir. 1993)). The court pointed out that "Venture Coal was entitled to challenge the Coal Sales Tax when it paid the taxes as much as were the plaintiffs in *Ranger Fuel*." *Venture Coal*, 370 F.3d at 1106.

None of the cases relied on by Novartis undercut *Venture Coal*. In each case, the "change in circuit precedent" that was found sufficient to justify equitable tolling related to the statute of limitations itself; in other words, the law changed in such a way that the petitioners' habeas filings, which would otherwise have been considered timely, no longer were. *See, e.g.*, *Shelton v. Purkett*, 563 F.3d 404, 407 (8th Cir. 2009) ("Because Shelton's petition was just barely timely under *Nichols*, it is clear that under the *Riddle* rule . . . Shelton's petition was untimely."); *Griffin v. Rogers*, 399 F.3d 626, 636 (6th Cir. 2005) ("This 30-day window was adopted by the *Palmer* Court in January 2002 . . . [y]et Griffin failed to file within this 30-day window in October 1998, over three years before the time frame was adopted in this circuit."); *York v. Galetka*, 314 F.3d 522, 528 (10th Cir. 2003) (allowing equitable tolling because petitioner filed his habeas petition over a year before the Supreme Court decision holding that pendency of federal habeas petition does *not* toll statute of limitations); *Harris v. Carter*, 515 F.3d 1051, 1055-56 (9th Cir. 2008) ("[Harris] filed successive petitions for state post-conviction relief while ensuring that enough time would remain to file a federal habeas petition under the

then-existing *Dictado* rule. The Supreme Court's overruling of the *Dictado* rule made it impossible for Harris to file a timely petition."). In these and other similar cases, equitable tolling was justified because the unforeseeable change in law made it impossible for the petitioners to file their petitions in a timely fashion. That is a far cry from this case. Novartis benefited from the change in law but it could have (as Wyeth did) attempted to effectuate that very change through a timely challenge to the PTO's PTA determinations.

In light of these considerations, even assuming that § 154(b)(4)(A) is not jurisdictional, the facts in this case do not justify the application of the equitable tolling doctrine to Novartis' nineteen untimely complaints.

C. Discovery Rule

As its final attempt to skirt the 180-day limitation of § 154(b)(4)(A), Novartis argues that its untimely complaints should be permitted under the discovery rule. The "discovery rule" provides that "a cause of action accrues when the injured party discovers—or in the exercise of due diligence should have discovered—that it has been injured." *Hardin v. Jackson*, 625 F.3d 739, 743 (D.C. Cir. 2010) (quoting *Nat'l Treasury Emps. Union v. FLRA*, 392 F.3d 498, 501 (D.C. Cir. 2004)).

This is nothing more than a rehash of Novartis' equitable tolling argument. Novartis claims that it did not discover that it had suffered an injury until a definitive federal court ruling was issued on the merits of its legal claims. (*See* Pls.' Mot. at 53-54.) For its *Wyeth* Claim, that ruling came from the Federal Circuit in January 2010. For its RCE Claim, however, no such court ruling has occurred to date and so Novartis suggests that it has not yet discovered any injury resulting from the PTO's actions.

As is the case with the equitable tolling doctrine, it can be debated as to whether the discovery rule even applies to § 154(b)(4)(A). The PTO suggests that because Congress specified that the statute of limitations would begin to run as of the date the patent was granted, Congress implicitly rejected the use of a discovery rule, whereby the statute of limitations would begin to run when the injury is first discovered by the injured party. (Def.'s Mot. at 24-25.)

However, as previously discussed, the Court need not resolve this question because it finds that the discovery rule, even if available under § 154(b)(4)(A), would not be applicable to this case. The injury that Novartis alleges is a procedural one—that the PTO misapplied the statutory procedure for PTA determination and harmed Novartis' interest in obtaining the full patent term to which it is entitled. However, as of the date that each patent was granted, Novartis knew the amount of PTA it had been awarded and knew what procedure the PTO had used in making that determination; all of the *facts* underlying Novartis' injury were both knowable and in fact *known* by Novartis as of that date. Thus, the 180-day limitations period began to run on that date, and Novartis' failure to challenge the PTA determinations within that 180-day period rendered nineteen complaints untimely.

The Court will now turn to the merits relating to the four patents (the '155, '518, '031, and '792 patents) as to which Novartis has raised timely claims.

III. RCE CLAIM

For three of the four timely-challenged patents, Novartis asserts that the PTO improperly calculated the amount of B Delay to which it was entitled under § 154(b)(1)(B). That section provides:

> [I]f the issue of an original patent is delayed due to the failure of the [USPTO] to issue a patent within 3 years after the actual filing date of the application in the

> United States, not including—(i) any time consumed by continued examination of the application requested by the applicant under section 132(b) . . . the term of the patent shall be extended 1 day for each day after the end of that 3-year period until the patent is issued.

35 U.S.C. § 154(b)(1)(B). As explained above, the PTO has promulgated a regulation interpreting § 154(b)(1)(B) as meaning: (1) that any time consumed by an RCE is excluded from the B Delay determination, even if it occurs after the three-year window has closed; and (2) that "time consumed by" an RCE extends until the issuance of the patent. *See* 37 C.F.R. § 1.703(b)(1). Novartis challenges both of these interpretations. Because the Court concludes that the PTO erred in excluding from B Delay time consumed by an RCE filed after the three-year window has closed, the Court need not address Novartis' alternative argument regarding the proper interpretation of "time consumed by" an RCE.

The PTO and Novartis disagree about the proper interpretation of § 154(b)(1)(B). Both parties agree that the statutory provision has two parts: a "trigger" provision and a "remedy" provision. First, it identifies a three-year period running from the date of the filing of the application. If a patent is not issued within that three-year period—the "trigger"—then the statute provides for a "remedy." The parties disagree, however, about whether the "not including" clause applies to the trigger or to the remedy.

The PTO has interpreted the "not including" clause to be a part of the remedy provision; in other words, if a patent has not issued within three years of its filing date, the patentee shall be entitled to a day-for-day patent term adjustment for every day until the patent issues, but "not including" any time consumed by an RCE. (*See* Def.'s Mot. at 33.) Novartis insists that the clause applies to the trigger. Under Novartis' view, if the patent is not issued within the three-year period, "not including" time consumed by an RCE, then the patentee is entitled to the day-

for-day remedy. (Pls.' Mot. at 21-22.) In other words, the filing of an RCE tolls the running of the three-year clock, but if the three-year clock runs out, the applicant would be entitled to a day-for-day patent term adjustment for every day until the patent issues, regardless of what activity occurred during that time—even an RCE. (*Id.*)

This exact issue was recently decided by the Eastern District of Virginia in *Exelixis, Inc. v. Kappos*, 2012 WL 5398876 (E.D. Va. Nov. 1, 2012). The issue in that case—as here—was "whether § 154(b)(1)(B) requires that, or even addresses whether, any PTA be reduced by time attributable to an RCE where, as here, the RCE is filed *after* the expiration of the three year guarantee period specified in that statute." *Id.* at *2 (emphasis added). Like Novartis, Exelixis argued that "the PTO improperly calculated B delay by not providing a day for day PTA for time consumed by the RCE filed after the three year period had expired." *Id.* at *5. And just as it did in this case, the PTO argued that "the time consumed by an RCE is always excluded from the calculation of B delay because, in the PTO's view, any time consumed by an RCE is subtracted from the PTA awarded under subparagraph (B), regardless of when the RCE is filed." *Id.*

Judge Ellis agreed with Exelixis' interpretation. First and foremost, he concluded that the plain and unambiguous language of § 154(b)(1)(B) makes clear that the three-year clock is tolled by the filing of an RCE, but that "once the three year clock has run, PTA is to be awarded on a day for day basis regardless of subsequent events." *Id.* at *6. In other words, the "not including" language of § 154(b)(1)(B) "clearly and unambiguously modifies and pertains to the three year period and does not apply to, or refer to, the day for day PTA remedy." *Id.*

Second, Judge Ellis noted that the plain meaning of § 154(b)(1)(B) was supported by that section's structure and purpose. Specifically, the statute is designed to provide compensatory

PTA for delays attributable to the PTO, while reducing PTA for delays attributable to the applicant. However, the filing of an RCE is not one of the listed categories of "applicant delay" provided for in § 154(b)(2)(C). Thus, Judge Ellis concluded that it was erroneous for the PTO to punish applicants for filing RCEs. *Id.* at *6-7.

Judge Ellis also thoroughly dispensed with the very arguments that the PTO has raised in this case. For example, in response to the PTO's insistence that its construction of § 154(b)(1)(B) should be entitled to *Skidmore* deference, Judge Ellis pointed out that "*Skidmore* deference is unwarranted, when, as here, the statute is unambiguous." *Id.* at *8. Similarly, he flatly rejected the PTO's argument that the plain language of § 154(b)(1)(B) renders the subsequent section—§ 154(b)(1)(C)—superfluous. *Id.* at *8 n. 16. And finally, Judge Ellis addressed the PTO's argument that Exelixis' proposed construction could lead to disparate treatment of some similarly-situated applicants, depending on which side of the three-year line the applicant files his RCE on. *Id.* In doing so, he reiterated the Federal Circuit's admonishment that, "[r]egardless of the potential of the statute to produce slightly different consequences for applicants in similar situations, this court does not take upon itself the role of correcting all statutory inequities." 591 F.3d at 1370. Judge Ellis also noted that it is within the PTO's power to minimize this disparate treatment by issuing timely notices of rejection such that RCEs must be filed within the three-year period. *Exelixis*, 2012 WL 5398876, at *8.

This Court finds Judge Ellis' well-reasoned opinion to be persuasive. It will therefore adopt his rationale for concluding that the PTO's interpretation is contrary to the plain and unambiguous language of § 154(b)(1)(B), and that it contravenes the structure and purpose of the statute.

Additionally, the Court notes one further consideration, not addressed by the parties in this case but raised by Abbott Biotherapeutics in *Abbott v. Kappos*, 10-cv-1853 (D.D.C.) that helps to bolster the conclusion reached here. Abbot notes that the PTO's position here—as embodied in 37 C.F.R. § 1.703(b)—is in conflict with another of the PTO's regulations. (*See* Plaintiff's Reply at 6-7, *Abbott v. Kappos*, No. 10-1853, July 18, 2012 [ECF No. 31].) Specifically, § 1.703(b) applies the "not including" language of § 154(b)(1)(B) to the "remedy" provision of that section. It states that:

> The period of adjustment under § 1.702(b) is the number of days, if any, in the prior beginning on the day after the date that is three years after the date on which the application was filed under 35 U.S.C. 111(a) . . . , but not including the sum of the following periods: (1) The number of days, if any, in the period beginning on the date on which an [RCE] was filed and ending on the date the patent was issued.

37 C.F.R. § 1.703(b). That section is therefore consistent with the PTO's position in this litigation: the "trigger" occurs if a patent is not issued within three years after the application's filing date, and the "remedy" consists of day-for-day PTA after that time, but does not include any time consumed by an RCE. (Def.'s Mot. at 32-33.)

However, that regulation is in tension with the immediately preceding PTO regulation, 37 C.F.R. § 1.702(b), which applies the "not including" language of § 154(b)(1)(B) to the "trigger" provision of that section and considers RCE in determining whether the three-year clock has run. It states:

> [T]he term of an original patent shall be adjusted if the issuance of the patent was delayed due to the failure of the Office to issue a patent within three years after the date on which the application was filed under 35 U.S.C. 111(a) . . . , but not including: (1) Any time consumed by continued examination of the application under 35 U.S.C. 132(b).

37 C.F.R. § 1.702(b). In other words, § 1.702(b) adopts the plain meaning of § 154(b)(1)(B), which is advocated by Novartis but disputed by the PTO in this case. It unambiguously provides that the three-year window will be tolled during the filing of an RCE, and says nothing about the remedy to be applied if and when that three-year mark is triggered. Thus, if both regulations were to be applied as written, time consumed by an RCE would apply to *both* the trigger and the remedy provisions of the statute, and would effectively result in the double-counting of the "not including" clause of § 154(b)(1)(B).

In response to Abbott's argument, the PTO appears to offer no explanation of the inconsistency between § 1.702(b) and its position in this litigation, or the inconsistency between § 1.702(b) and § 1.703(b). Instead, the PTO ignores both the plain language of the statute and the text of § 1.702(b) and advocates an inconsistent interpretation of § 1.703(b). These apparent inconsistencies further bolster the Court's view that the PTO's interpretation of § 154(b)(1)(B) is contrary to law.

In sum, the PTO's interpretation of § 154(b)(1)(B) contravenes the plain meaning of the statutory language and therefore must be set aside as "not in accordance with law" and "in excess of statutory . . . authority" pursuant to 5 U.S.C. § 706(2)(A) and (C).

IV. *WYETH* CLAIM

In *Wyeth*, the Federal Circuit held that the PTO's interpretation of § 154(b)(2)(A) regarding the calculation of A/B Delay Overlap was improper. *See* 591 F.3d at 1372. After the Federal Circuit's ruling, the PTO announced that it would not seek further review of the decision and would use the proper method of calculating A/B Delay Overlap both going forward and for patents issued before March 2, 2010, so long as the request for recalculation was filed within 180

days of the issuance of the patent.[3] (AR166-175). Novartis argues that the PTO's decision not to apply the post-*Wyeth* calculation method to the patents issued before September 2, 2009 was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. (Pls.' Mot. at 17-18.) Although Novartis initially alleged that eleven of the patents at issue in this case were entitled to additional PTA because of the PTO's failure to apply *Wyeth*, only one of those patents—the '792 patent—was timely challenged in this Court.

As an initial matter, it is noteworthy that the PTO failed to respond to Novartis' *Wyeth* claim, so the Court may treat this argument as conceded. *See Day v. D.C. Dep't of Consumer & Regulatory Affairs*, 191 F. Supp. 2d 154, 159 (D.D.C. 2002).

Regardless, under the PTO's own policy, the *Wyeth* method of calculating A/B Delay Overlap should have been applied to the '792 patent. Specifically, on March 10, 2010, the PTO wrote a letter to the Patent Public Advisory Committee in which it explained its position on the application of *Wyeth* to previously-issued patents. The PTO explained:

> The USPTO is acting consistent with the judicial review provisions of 35 U.S.C. § 154(b)(4) in limiting patent term adjustment recalculations to patentees who either: (1) filed a request for patent term adjustment recalculation that has not yet been decided within the 180-day period in 35 U.S.C. § 154(b)(4); or (2) are currently engaged in a challenge, in the USPTO *or the courts*, to the USPTO's patent term adjustment determination that was commenced within the 180-day period in 35 U.S.C. § 154(b)(4).

[3] Novartis asserts that this effectively set the cut-off date for recalculation at September 2, 2009. However, it appears to the Court that the post-*Wyeth* interpretation was actually available to patents issued on or after August 1, 2009. The policy discussed above was announced in the Federal Register on February 1, 2010; thus, for any patent issued on or after August 1, 2009 (180 days prior to that announcement), the patentee would have been able to seek reconsideration of its PTA determination. Regardless, the PTO has not disputed Novartis' characterization of its policy. Moreover, only one of the patents at issue in this case was granted in the window between August 1 and September 2, 2009—U.S. Patent No. 7,576,221—and as the challenge to that patent was not timely filed, this appears to be a distinction without a difference.

(AR183 (emphasis added).) Novartis first filed a complaint in this Court regarding the '792 patent on June 30, 2009. (*See Novartis v. Doll*, 09-1203 [ECF No. 1] (D.D.C. June 30, 2009).) As explained above, although that complaint was not filed within 180 days of the issuance of the '792 patent, it was filed within 180 days of the PTO's denial of its request for reconsideration. Thus, under normal tolling rules, which this Court has held apply to § 154(b)(4), at the time of the Federal Circuit's *Wyeth* decision, Novartis was "currently engaged in a challenge, in . . . the courts, to the USPTO's patent term adjustment determination that was commenced within the 180-day period in 35 U.S.C. § 154(b)(4)." (AR183.) The PTO's refusal—with no explanation whatsoever—to follow its own policy and apply *Wyeth* to the '792 patent contravenes the APA. In particular, the PTO failed to consider the relevant factors and to "articulate[] a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made,'" as required by the arbitrary and capricious standard. *Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43 (quoting *Burlington Truck Lines v. United States*, 371 U.S. 156, 168 (1962)).

In addition to violating its own policy, the PTO's refusal to apply *Wyeth* to the '792 patent is contrary to well-established law. The '792 patent was issued on December 30, 2008, a full two months after the district court opinion in *Wyeth*. 580 F. Supp. 2d 138. Novartis sought agency reconsideration of its PTA determination in February 2009, in part based on the district court's *Wyeth* ruling. (A1011-14.) In June 2009, the PTO declined to apply the *Wyeth* method of calculating overlap to the '792 patent. (A1015-21.) This was erroneous. The Supreme Court has made it clear that it is "error to refuse to apply a rule of federal law retroactively after the case announcing the rule has already done so." *James B. Beam Distilling Co. v. Georgia*, 501 U.S. 529, 540 (1991). The district court's *Wyeth* opinion was applied retroactively to Wyeth;

Wyeth's patent terms were adjusted in accordance with the newly-announced rule in that case. Thus, when Novartis filed for reconsideration almost five months later, the PTO abused its discretion by refusing to calculate Novartis' patent consistently with the method adopted in *Wyeth*. Its decision to do so "violate[d] the principle of treating similarly situated parties the same." *Nat'l Fuel Gas Supply Corp. v. FERC*, 59 F.3d 1281, 1289 (D.C. Cir. 1995).

For these reasons, the Court finds that the PTO erred in not applying either this Court's or the Federal Circuit's *Wyeth* decision to the '792 patent.

V. FIFTH AMENDMENT TAKINGS CLAIM

As its final argument, Novartis asserts that by applying its erroneous interpretations of § 154(b)(1)(B), the PTO deprived Novartis of its property interest in its patent term without compensation in violation of the Takings Clause of the Fifth Amendment. (Pls.' Mot. at 54.)

With respect to the nineteen patents for which Novartis did not timely challenge the PTA determinations under § 154(b)(4)(A), this argument is untimely and cannot now be raised.

Moreover, the Court need not address this argument as it relates to the remainder of Novartis' patents. With respect to Novartis' RCE Claim, this argument is moot, as the Court has already ordered the very remedy that Novartis seeks. Specifically, this Court ruled that the PTO's refusal to award B Delay for time consumed by an RCE filed after the three-year deadline was erroneous and ordered the PTO to recalculate the PTA determinations for three of Novartis' patents. (*See supra* Section III.) Similarly, the Court has already ruled that the PTO acted arbitrarily and capriciously in not applying the *Wyeth* method of calculating A/B Delay Overlap to the '792 patent, and has ordered the PTO to recalculate the PTA determinations for that patent.

(*See supra* Section IV.) Thus, the Court need not determine whether either of the PTO's errors amounted to a constitutional violation.

CONCLUSION

For the reasons stated above, plaintiffs' motion for summary judgment is granted in part and denied in part, and defendant's motion for summary judgment is granted in part and denied in part. A separate Order accompanies this Memorandum Opinion.

/s/
ELLEN SEGAL HUVELLE
United States District Judge

DATE: November 15, 2012

EXHIBIT 5

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
Alexandria Division

EXELIXIS, INC.,	)	
Plaintiff,	)	
	)	
v.	)	**Case No. 1:12cv96**
	)	
HON. DAVID J. KAPPOS, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office,	)	
Defendant.	)	

ORDER

For good cause,

It is hereby **ORDERED** that the memorandum opinion (doc. 29) is **AMENDED** to insert the following footnote on page 14 at the end of the sentence that reads, "The short and dispositive answer to this argument is that the word "then" does not appear in the statute and the PTO's insertion of the word in its reading is not a construction of the provision but rather a rewriting of it":

> Footnote: Nor is the legislative history of any avail to the PTO; this history does not expressly address the question presented and is, at best, ambiguous. Fairly read, the legislative history simply repeats what subparagraph (B) clearly states. See H.R. Rep. No. 106-464, at 126 ("Any periods of time . . . consumed [by an RCE] . . . shall not be considered delay by the USPTO and shall not be counted for purposes of determining whether the patent issued within three years from the actual filing date"). In any event, legislative history, however interpreted, cannot trump clear and unambiguous statutory language. *See Mohamed v. Palestinian Authority*, 132 S.Ct. 1702, 1709 (2012) ("reliance on legislative history is unnecessary in light of the statute's unambiguous language") (internal quotation marks and citation omitted); *United States v. Gonzales*, 520 U.S. 1, 6 (1997) ("Given the straightforward statutory command, there is no reason to resort to legislative history.").

In all other respects, the memorandum opinion remains unchanged.[1]

The Clerk is directed to send a copy of this Order to all counsel of record.

Alexandria, VA
November 6, 2012

T. S. Ellis, III
United States District Judge

[1] The footnote being added was omitted inadvertently.